A STUDY ON THE PREVALENCE OF CATAMENIAL EPILEPSY – AN ELUSIVE CONDITION

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON THE PREVALENCE OF CATAMENIAL EPILEPSY – AN ELUSIVE CONDITION"** is a bonafide record of work done by **Dr.M.KAVITHA** in the Institute of Neurology, Rajiv Gandhi Government General Hospital & **MADRAS MEDICAL COLLEGE, CHENNAI** in partial fulfillment of the Tamilnadu Dr.MGR Medical University rules and regulations for the award of **D.M. (NEUROLOGY)** degree under my direct guidance and supervision during the academic year **2011-2014**.

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DECLARATION

I solemnly declare that this dissertation titled "A STUDY ON THE PREVALENCE OF CATAMENIAL EPILEPSY – AN ELUSIVE CONDITION" is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof. Dr. K. BHANU, Dip. NB., D.M., Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology**.**

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Introduction

INTRODUCTION

Epilepsy is a commonly encountered neurological condition characterised by recurrent episodes of unprovoked seizures. Epilepsy acts as a broad terminology that includes any abnormal mechanism in brain which cause an electrical short circuit or electrical storm that manifests as seizure[1]. Epilepsy affects both adults and children. The terminology "Epilepsy" has been used since 500 BC which literally means "to attack or assault". In ancient times, people with epilepsy were considered as being possessed by evil spirits and it was called "the sacred disease". Theories on the etiology of epilepsy had been multidimensional from invasion by demons to shifting lunar phases. So it is evident that since olden days the association between seizures and cyclicity and between epilepsy and gender had been suspected but on different grounds from our understanding today. Epileptic seizures can occur with wide variation in presentation and to provide effective appropriate treatment, systematic precise classification of epilepsy is mandatory. The widely used currently valid ILAE classification of epileptic seizures was proposed in 1981 which is based on EEG and semilogy. Seizures are mainly divided into partial and generalized seizures, but some are unclassified[1].

There are certain types of epileptic seizures which occur in clusters during a particular period. The classical example of them is Catamenial epilepsy. The word "catamenial" is derived from a greek word "Katamenios" which means monthly[2]. Antyllus, who was a contemporary of Galen and one of the eminent surgeons of ancient times, wrote, "… the moon rather moistens, and for this reason it makes the brain relatively liquid and the flesh putrid which renders the bodies of people who live in a clear, cold air moist and dull and for the same reason stirs up heaviness in the head and epilepsies"[2]. During middle ages, a vapour emanating from the uterus was believed to be triggering the seizures. At a conference in Royal Medical and chirurgical society in 1857, Sir Charles Locock was the first to describe the association between seizure clusters and menstrual cycle. He named that as Hysterical epilepsy (from the greek word "Hystera" which means "uterus") which occurred only in women and he also noted the regularity of recurrence associated with the menstrual cycle. Gowers presented one of earlier collection of menstruation cycle related seizure clusters affecting about forty six among eighty two women in 1881[3].

The common definition of catamenial epilepsy is, "the seizure clusters occurring around menstrual cycle or an increased seizure frequency during certain phases of menstrual cycle"[4]. Some female sex hormones and certain steroid gonadal hormones have neuroactive properties that can

trigger seizures. Though there are many subtypes in catamenial epilepsy, neurosteroids have been found to influence the seizure clusters in women who have normal 28 day menstrual cycles who suffer during the perimenstrual period. It is thought that progesterone derived neurosteroids withdrawal causes enhanced stimulation or excitability of cerebral cortex which predispose to seizures. Varied concentrations of anticonvulsants during the different phases of menstrual cycle also cause increased seizure susceptibility[5].

Catamenial epilepsy has been observed in 10% - 70% of epileptic women with recurrent exacerbations[6]. There is a wide percentage of prevalence of catamenial epilepsy as reported by many studies due to self-observed reports, seizure-menstrual cycle diaries of women with pharmacoresistant and refractory epilepsy[6]. But this entity has gained much attention and awareness though there is no lucid or globally accepted criteria for diagnosing catamenial epilepsy.

Aim of Study

AIM

1. To assess the prevalence of catamenial epilepsy among women attending epilepsy clinic of our institution.

2. To classify the women with catamenial epilepsy according to the phase of menstrual cycle in which the seizure clusters occur

3. To analyse the seizure dispersion during menstrual cycle in women with recurrent epilepsy.

4. To assess the serum estradiol and serum progesterone level of women with recurrent seizures during mid-luteal phase of the menstrual cycle.

Review of the Literature

REVIEW OF LITERATURE

THE GONADAL HORMONES

OESTROGENS

Oestrogens are produced in both ovarian and extraovarian tissues. The principal oestrogen synthesised in ovary is 17 beta oestradiol. The oestradiol is predominantly synthesised in granulosa cells of ovaries. Oestrogens are produced by the mechanism of aromatization of androgens. When these enzymes have hyperactivity it causes "oestrogenization". Oestrogens promote the tissues involved in reproduction to develop and the vaginal epithelium and uterine endometrium to proliferate. The myometrium becomes mature and the ducts of breasts proliferate. Oestrogens aid in the anabolic effect on bone and cartilage thereby promoting growth. They are also important for the development of secondary sexual characteristics of female[7].

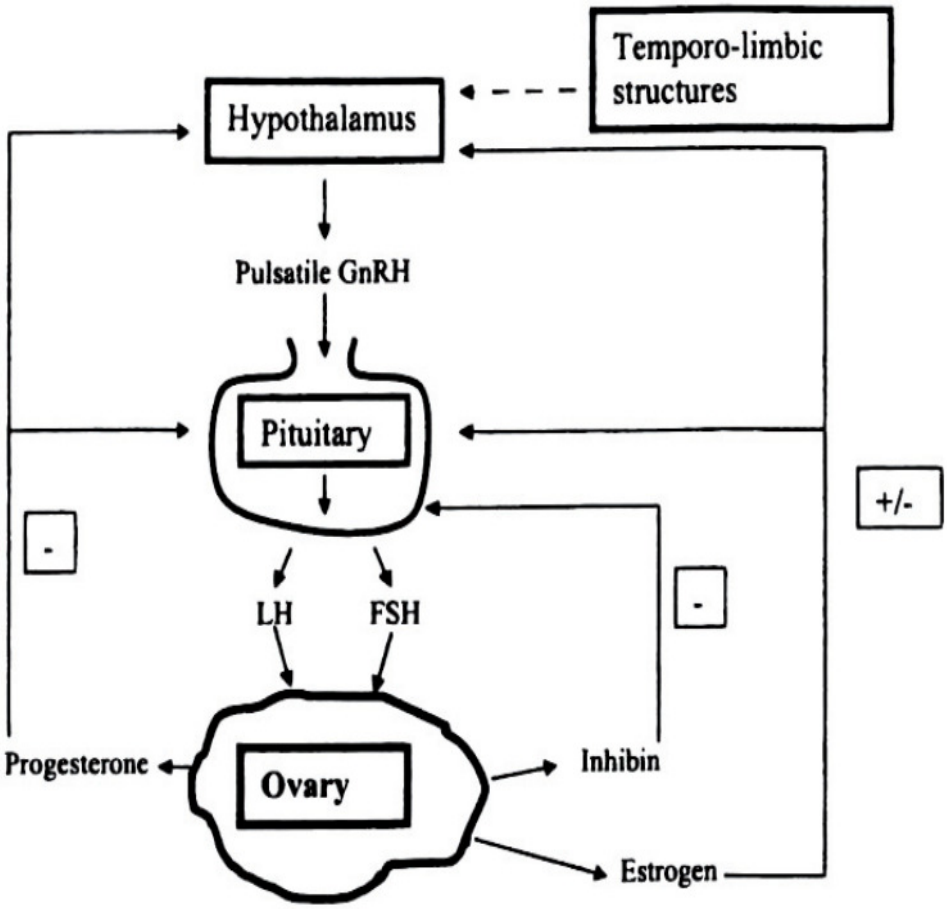
PROGESTERONE

Progesterone is produced and secreted by corpus luteum. It is metabolised in the liver. It requires concurrent action of oestradiol for appropriate effect. Progesterone aids in reduction of vaginal epithelial

proliferation and thus converts the proliferative uterine epithelium to become secretory. The development of acinar part of breast glands is stimulated by progesterone[7].

PUBERTY

From the eighth year of life in women, there is a gradual progressive increase in the pituitary gonadotropic hormones thereby causing menarche which occurs usually between 11 and 16 years of age[7].

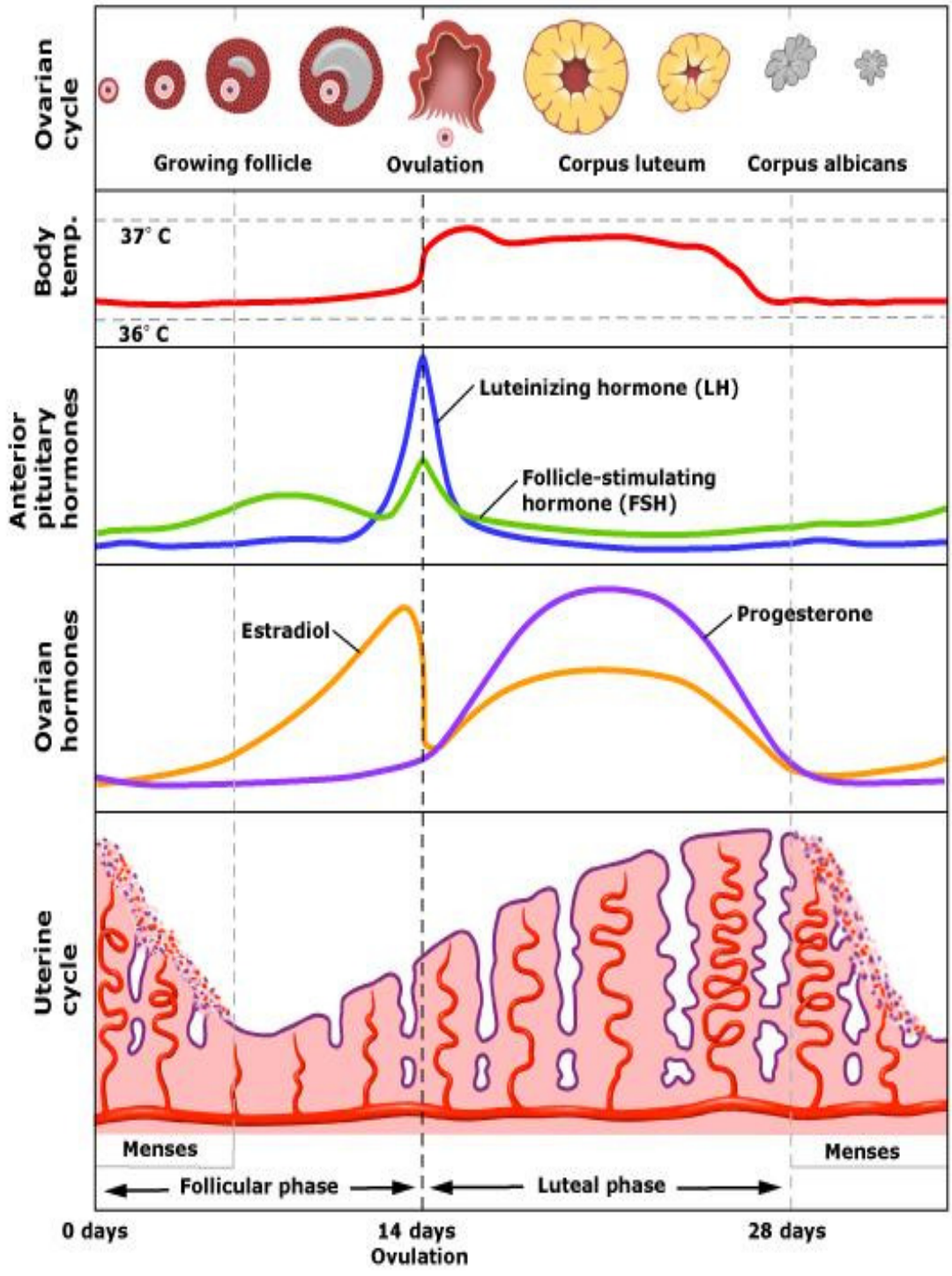


THE MENSTRUAL CYCLE

Once menarche is attained, the menstruation occurs in a regular cyclical pattern. GnRH, the hormone secreted from the hypothalamus in pulses every 1 to 2 hours intervals. GnRH stimulates the release of pituitary hormones. The menstrual cycle usually occurs as 28 day cycle but may range from 21 to 35 days. On day 1, the menstrual bleeding occurs and continues for about 5 days. At the same time, the follicular phase starts and the endometrium slowly progresses inorder to receive a fertilized ovum. The follicle undergo maturation under the influence of FSH. The blood supply to ovaries increases and the follicle that undergoes maturation produces oestradiol in increased amount.

On day 13, the concentration of oestradiol reaches peak and by positive feedback mechanism the GnRH and LH is secreted. This causes LH to reach its peak for the ovulation to occur. During this time, the body temperature increases by about 0.5 degree Celsius. The luteal phase occurs between days 14 and 28 of the menstrual cycle. During the luteal phase the corpus luteum is formed. The corpus luteum mainly produces progesterone and to some extent oestradiol also. If pregnancy does not occur, the corpus luteum gradually involutes. During days 27 and 28 of menstrual cycle, there is decrease in oestradiol and progesterone secretion. Then the spiral

arterioles undergo constriction . so the endometrium undergo ischemia and desquamation thus causing menstruation[7].



INFLUENCE OF HORMONES ON EPILEPSY

The gonadal hormones have been found to have different effects on the susceptibility of seizures in women. Their effects are described below:

OESTRADIOL

According to Logothetis and Harner (1960) , " the oestradiol administration to ovariectomized rats resulted in proconvulsant effects". The studies done earlier depict that the oestrogens act on the cerebral cortex directly and lead to epileptogenic effects[8]. Similar studies were done by Woolley and Temiras (1962), Marcus et al (1966). Nicoletti et al, (1985) and Woolley (2000) in their study hypothesised, " oestradiol also potentiates seizures triggered by pentyletetrazol[9] . Smith and his colleagues along with Wong and Moss (1994) proved the excitatory effects of oestrogens which can be partially explained by their ability to enhance glutamate-receptor excitatory neurotransmission and decrease gamma amino butyric acidergic inhibition. The oestradiol has direct action of neurons in the limbic system, cerebral cortex and the parts of brain that has increased seizure susceptibility[10]. Thus oestrogen has pro-convulsive effect and this is thought to be the cause of variation in seizure propensity during different phases of a woman's life after menarche.

PROGESTERONE

Hans Selye et al first identified the anticonvulsant effect of progesterone in the PTZ test during 1942[10]. Many similar studies on both animals and humans, were then published later on the anticonvulsant properties of progesterone by Craig and Deason (1968), Landgren et al (1978), Herzog (1995), Lonsdale and Burnham (2007), Tauboll et al (1993)[11]. The progesterone and its metabolites have influence over the brain excitability by acting though steroid receptor or GABA receptor- chloride ionophore complex. The progesterone with its metabolites act similar to barbiturates but the site of action is not the same. Barker et al has shown," the steroids prolong the effective open time of chloride channels, thereby inhibiting the excitation of neurons". So progesterone affects the excitatory ability of brain along with GABA effect. Smith et al (1987), "after systemic or topical application of steroid in purkinje cells from cat, both progesterone and several metabolites decreased glutamate responsiveness."[12] According to Mattson et al (1984) and Herzog (1995), progesterone therapy has been beneficial in the treatment of catamenial epilepsy.[13]

DEFINITION AND PATTERNS OF CATAMENIAL EPILEPSY

Catamenial Epilepsy is defined as cyclical increase in seizure frequency during or around the time of menstrual periods. Duncan et al (1993) defined, "Catamenial epilepsy as having 75% of seizures during a 10 day period of menstrual cycle beginning 4 days before menstruation". Newmark and Penry (1980) defined, " perimenstrual catamenial epilepsy as epileptic seizures occurring in women of fertile age exclusively or significantly more often during a 7-day period of the menstrual cycle, beginning 3 days before menstruation and ending 4 days after its onset"[14]. Herzog et al. (1997) defined, " catamenial epilepsy as a greater than average seizure frequency during perimenstrual or periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles"[14]. All the above definitions are arbitrary, not definite, variable and less uniformity in definition. According to Reddy (2007), "a two-fold or greater increase in seizure frequency during a particular phase of the menstrual cycle may be defined as catamenial epilepsy"[15]. This explanation can be used as a standard criterion in studies to analyse the pathophysiology and treatment of catamenial epilepsy. By using this criteria, about one third of women with intractable epilepsy would be classified under the category of catamenial epilepsy. By adopting a standard nomenclature, greater uniformity may exist

in studying the pathogenesis and treatment of catamenial seizure exacerbation.

Herzog et al, in his study classified catamenial epilepsy into three patterns:

1. Perimenstrual (C1) – Days -3 to 3
2. Periovulatory (C2) - Days 10 to -14
3. Luteal (C3) - Days 10 to day 3

"In the above classification , Day 1 denotes the first day of menstrual flow and ovulation is presumed to occur 14 days prior to onset of the next cycle (-14). The above mentioned patterns were demonstrated by charting the menses and seizure occurrence and estimating the mid-luteal serum progesterone level to differentiate between normal and inadequate luteal phase cycles (<5ng/ml).

Seizure exacerbation around the time of menstruation or ovulation occurs in women with normal menstrual cycles"[16]. Women with abnormal menstrual cycles may have exacerbation in the luteal phase of the menstrual cycle. This pattern is very difficult to identify because the time of seizure exacerbation is prolonged and not focused. These women have anovulatory cycles and inadequate luteal phase syndrome. As they do not ovulate, there is no corpus luteum (derived from the egg leaving the ovary) formation during the luteal phase of the menstrual cycle and hence progesterone is not

secreted.The changes in oestrogen and progesterone levels during the menstrual cycle influence the seizure pattern in epileptic women. In fact, the neuronal excitability is affected by oestrogen and progesterone. In many men and women, seizures do not occur in a random manner. There exists a tendency for the seizures to occur in clusters in about 50% of epileptic patients. The seizure clusters occurring with a specific periodicity in relation to the menstrual cycle, is called Catamenial Epilepsy. This may occur due to the neuroactive steroid hormones and the rhythmic variation of the gonadal hormonal levels. So the gonadal hormones secreted during menstrual cycle have effect on the cluster of seizures. The seizure frequency during the ovulatory cycles has a direct proportional association with serum estradiol/progesterone ratio. The ratio is at its peak before ovulation and during menstruation. The ratio is low at early and middle of the luteal phase of menstrual cycle. The seizure clusters during the premenstrual period is due to the withdrawal of progesterone. In catamenial epilepsy, the seizures tend to occur during particular phase of menstrual cycle. The increased seizure frequency during the period just prior to menstruation is the commonest type of catamenial epilepsy. The alterations caused by oestrogen as well as progesterone in catamenial epilepsy has been studied and published by many investigators. But there lie many controversies and differences of opinion in the proposed pathogenesis of catamenial epilepsy.

Assessment of the levels of oestrogen and progesterone in epileptic women with catamenial exacerbation is important. Though the proconvulsive effect estrogen is known, Logothetis et al., in his study could not confirm the suggestion that increased levels of estrogen are the cause of catamenial exacerbation by estimating the ovarian hormone levels during the menstrual cycle of epileptic women. Pennell et al also could not substantiate the association between the seizure clusters and the serum levels of oestrogen and progesterone in women with perimenstrual seizures. But there are a few studies which have demonstrated the significant reduction in the frequency of epileptiform discharges with intravenous progesterone infusions in a few patients[17]. All these studies emphasise the need of analysing the exact action of estradiol and progesterone in women with catamenial and non-catamenial epilepsy.

The prevalence of catamenial epilepsy occurs between ten and seventy percentage of epileptic women. This wide range is because of the lack of specific criteria to define catamenial epilepsy. However, the ideal definition of catamenial epilepsy would be, the seizure clusters occurring during or around the time of menstruation. It can occur in any type of seizures.

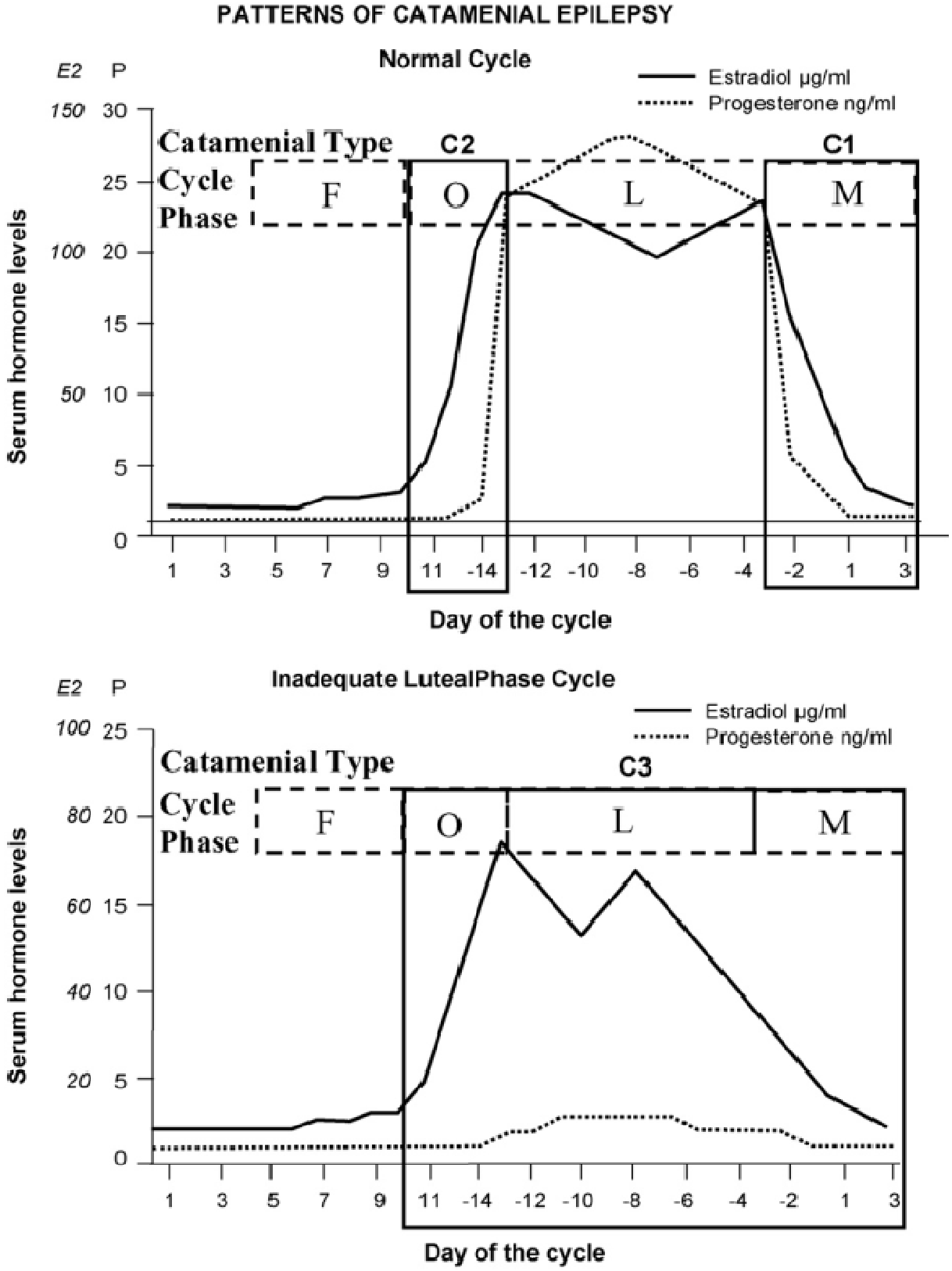
The wide range of prevalence may be due to the criteria of analysis that differs which includes cyclical pattern noted by the patients themselves, the seizure clusters noted down in the menstrual cycle-seizure dairy adviced to be maintained by the patients and other vague details of seizures occurring during the middle of the menstrual cycle which could be due to the increase of oestrogen levels before ovulation, without increase in progesterone level till ovulation. Actually Seizures do not occur during the middle of the luteal phase as the levels of progesterone are high.

Herzog et al had studied on catamenial epilepsy and the classified three distinct patterns of catamenial exacerbation :

1. Perimenstrual (C1 – days -3 to 3)
2. Periovulatory (C2 – days 10 to 13) in normal menstrual cycle
3. Luteal (C3 – days 10 to days -3) in inadequate luteal phase cycles

In this classification, day 1 is the first day of menses and in normal menstrual cycle ovulation is presumed to occur in and around fourteen days prior to the onset of subsequent cycle. The following are the ways to demonstrate these three patterns of catamenial epilepsy :

1. Noting down the dates of menses and the seizures
2. Assessing the serum progesterone levels during the luteal phase to differentiate between normal and abnormal luteal phase.


PATTERNS OF CATAMENIAL EPILEPSY
Normal Cycle
E2 P
Estradiol µg/ml
Progesterone ng/ml
Catamenial Type
Cycle
Phase
C2
C1
F
O
L
M
Serum hormone levels
Day of the cycle
Inadequate LutealPhase Cycle
C3

PATHOPHYSIOLOGY

Catamenial epilepsy is believed to occur due to rhythmic and cyclic variations of the gonadal hormone levels and the drug metabolism. The epileptic women with catamenial exacerbation have their seizure clusters at or shortly after menarche. They show excessive EEG activity during the menstrual cycle. Oestrogen increases the seizure propensity and Progesterone decreases it. Progesterone and estrogen influences the development and plasticity of neurons in diffuse cerebral and brainstem areas by regulating the synthesis, release and transport of certain neurotransmitters like GABA, glutamate and by altering the brain excitability[18]. Particularly during two specific times of menstrual cycle, the seizure cluster frequency increases, during the days prior to menses when progesterone level is low and then before ovulation when the oestrogen level is high. The frequency of seizures also increases when the cycles are anovulatory during which time the progesterone levels are again low. In women with normal ovulatory cycles, the increased values of estradiol and progesterone ratio prior to the onset or during menstruation may be the reason behind the seizures. When the progesterone action no longer exists, same as that when benzodiazepines are stopped suddenly in a patient with epilepsy, the seizure exacerbation might occur in the premenstrual period. During the time before ovulation, the levels of oestradiol increase and this

might lead on to seizure exacerbation during the periovulatory period. The luteal phase is free of seizure or rarely the seizures occur as the progesterone is at its peak compare to oestrogen. During anovulatory cycles, the luteal phase has low levels of progesterone and so the seizure frequency hikes up during the premenstrual period as the oestrogen level increases during the middle of menstrual cycle but without increase in progesterone level. In some healthy women with normal menstrual cycle, 8-10% has anovulatory cycles. Several studies suggest the presence of different types of cyclic rhythmic pattern of seizures in women. So, the type of treatment option for catamenial epilepsy also differ and depend upon the exact phase of the menstrual cycle the seizure clusters occur.

According to Quigg et al, the seizure frequency may also be influenced by age of the patient as age has modulatory effect on the hypothalamic-pituitary-gonadal axis through various external factors the patients are exposed[19].

Pregnanolone, the endogenous neurosteroid level may decrease when the progesterone levels decrease before menstruation thereby decreasing the GABAergic effects and causing seizure exacerbation.

According to Rosciszewka, Bunter, Guz and Zawisza (1986) , “the seizure incidence during the menstrual cycle is connected with a deficit of

progesterone rather than elevated oestrogen levels. The lowest number of seizures was noted when progesterone reached its highest level"[21]. The progesterone due to its protective effect on brain may be the strategy to be used to treat catamenial epilepsy. Females with so-called catamenial epilepsy had premenstrual tension more frequently. This difference is connected with greater hormonal disturbances and changes in water electrolyte balance.

The serum levels of anticonvulsants also fluctuate at different phases of menstrual cycle. The decrease in levels of phenytoin and the association with increased seizure frequency have been demonstrated during menstrual cycle. The reduction of oestrogen and progesterone could enhance the production of the monooxygenase enzymes in liver thereby increasing the seizure propensity. During the times of seizure exacerbation the serum levels of anticonvulsants may be measured and alteration in the dosage accordingly may be made to achieve seizure control.

EFFECTS OF OESTROGENS

The oestrogens have proconvulsant properties in animals and humans According to Terasawa and Timiras, “in female mice the threshold level of seizures arising from limbic structures are correlated to the levels of estrogen which is evidenced by the enhancement of epileptiform spike and wave discharges occurring spontaneously after administration of estradiol. During regular menstrual cycles, the seizure threshold has been found to be low in hippocampal regions and more in the amygdala.” [22] The pathophysiology behind the neuronal excitability caused by estradiol is not clearly understood. According to some experimental studies , the action of oestrogen on altering the seizure threshold has been influenced by many factors like age of the patient, the nature of the receptors of different gonadal hormones.

The major biological effects of estrogen occurs through two different oestrogen receptors, ER alpha and ER beta. Estradiol alters the axonal plasticity and therefore the number of dendritic spines in the hippocampus increase. This causes increased release of mRNA for NMDA receptors thereby increasing the excitability of NMDA receptors .So the amount of calcium that enters increases which is enhanced by the NMDA receptors that are excitatory. The estradiol decreases the Glutamic acid decarboxylase

(GAD) causing dysregulation of the GAD, which is an important enzyme in conversion of glutamate to GABA. Thus, there is enhanced excitatory effect in seizure vulnerable regions due to exposure to estradiol.

In many studies on humans, the direct correlation between the clustering of seizures and the oestrogen progesterone serum levels which is high during the perimenstural and around the time of ovulation and low during the middle of the luteal phase, have been demonstrated. Logothetis et al, demonstrated that the premenstrual increase in seizure frequency by intravenous oestrogen injections given to epileptic women showed interictal spike and wave discharges in EEG[22]. This proves that the facilitatory effect of oestrogen is responsible for the catamenial seizure exacerbation. In few recent researches the scientists used conjugated synthetic oestrogen derived from equine sources. The equine oestrogen conjugated with alpha estradiol could not show similar exacerbation of seizures. Till early luteal phase of menstrual cycle the mid cycle increased level of oestrogen without concurrent increase of progesterone is attributed to periovulatory catamenial exacerbation. The premenstrual increase in the ratio of estrogen and progesterone level is partly responsible for perimenstrual seizure clusters. El-khayat et al also proved the presence of higher progesterone levels in the perimenstural period and low ratio of oestrogen and progesterone in women with catamenial exacerbation. He also demonstrated increased frequency of

epileptiform discharges in EEG during menstruation in these women[23]. Estradiol is hypothesised to have influence on the anovulatory cycles but the true mechanism of the oestrogens on this entity is not understood clearly. According to Osborne and Frye, oestrogen acts by increasing the 5 alpha pregnanolone, a metabolite of progesterone in the hippocampus and could possibly have an anticonvulsant action. They implanted some wild mice with silastic estradiol capsules and did oophorectomy for all those mice thereby depleting the 5alpha reductase and then gave intraperitoneal injections of pentylenetetrazol (PTZ). They injected the 5 alpha reductase with estradiol in certain other ovariectomised mice and then gave PTZ injections. Mice with depleted 5 alpha reductase had seizures[24]. Estradiol has influence on GAD and also in the expression of neuropeptide.

EFFECTS OF PROGESTERONE

Many studies done on animals and humans demonstrate the association of catamenial seizures and the decrease in progesterone level before and after menstruation.

Progesterone is believed to decrease the neuronal firing and the epileptiform discharges. In human studies, progesterone has been found to decrease seizure frequency. In the mid-luteal phase , when the serum progesterone levels the seizures decrease. Alterations in serum

progesterone levels have been directly proportional to occurrence of catamenial seizures.

According to a recent study which involved transcranial magnetic stimulation in analysing the alterations in the cerebral excitability during the menstrual cycle, both ovulatory as well as anovulatory could not prove the negative effect of progesterone on the excitability of neurons in mice. There were no notable differences in the parameters of transcranial magnetic stimulation when the progesterone levels were low during menstruation and rise in levels during the luteal phase of the cycle.[25]

The biological actions of progesterone are facilitated by the progesterone receptors (PR) which belong to the nuclear receptor group of transcription factors. But the anticonvulsant properties of progesterone are not linked to the progesterone receptors. The anticonvulsant property of progesterone was not decreased in the mice where the progesterone receptors were destroyed by mutation of the progesterone receptor gene. The allopregnanolone which is a metabolite of progesterone had been observed to have anticonvulsant. So the role of the progesterone receptors in the propensity of seizures is not fully established. There is a increase in the amount of dendritic spines during the initial period of exposure and then there is a fall in the hippocampal dendritic spines and excitatory synapses.

Progesterone has antagonistic actions against oestrogen by reducing the number of estrogen receptor number[26].

NEUROSTEROIDS

Allopregnanolone is the 3 alpha hydroxylated, A-ring reduced metabolite of progesterone. (3 alpha hydroxyl 5 alpha pregnane – 20-one). The allopregnanolone and the allotetrahydrodeoxycorticosterone (allo-THDOC) are most effective among the numerous endogenous neuroactive steroids which has potent effect on membrane excitability. Allopregnanolone has no effects as hormone but together with allo-THDOC acts as endogenous brain excitability regulator which has anxiolyic, sedative and anticonvulsant properties. Allopregnanolone and allo-THDOC cause hyperpolarization of the hippocampal and other neurons by GABA mediated inhibitory effects. Allopregnanolone has similar binding capacity as that of benzodiazepine , flunitrazepam, etc. Progesterone, which is the parent steroid stimulates GABA –induced chloride currents at peak level. Among women, the allopregnanolone level correlates well with the progesterone serum level during the menstrual cyle and pregnancy. Anyway the action of progesterone and allopregnanolone on brain does not only rely upon the extra-cerebral production as they are produced in brain themselves. They are produced in cortex and hippocampus. But the allo-THDOC is synthesised only in the adrenal gland. Allopregnanolone , allo-THDOC along with

other endogenous and synthetic neurosteroids had been demonstrated to have anticonvulsant properties against pentylenetetrazol, bicuculine, and kainicacid- induced seizures and against status epilepticus. But they are not effective against electric shock and seizures caused by strychnine. Allopregnanolone has less toxicity than clonazepam though the action in same comparatively less effective. The potent action during the middle of the luteal phase at the GABA A receptor may be due to the enhanced production of delta GABA a receptor subtype by progesterone. The GABA A receptor does not respond to benzodiazepines in the late diestrus part due to rapid withdrawal of progesterone but not to allopregnanolone . This mechanism could be inhibited by the alpha 4 subunit of the GABA A receptors. On the contrary, few sulphated neuroactive steroids increase neuronal excitability. They are pregnenolonesulfate and dehydroepiandrosteronesulfate (DHAS). They cause negative modulation of GABA A receptor thereby increasing the neuronal firing and there is also NMDA receptor excitation by glutamate. The DHEAS levels are decreased by the enzyme-inducers like phenytoin and carbamazepine[27].

Neurosteroids effectively modulates the GABA A receptors function particularly the allopregnanolone. So the perimenstural seizure clusters might be due to the withdrawal of the anticonvulsant action of neurosteroids. Further due to the withdrawal of the neurosteroids the GABA

A receptor alpha 4 subunit in the hippocampus increased with reduced GABA gated current thereby increasing seizure propensity and there is significant changes in the resistance to several groups of anticonvulsants.

The recently discovered growth factor response factor -3 (Egr 3) is believed to have a significant role in the alpha 4 subunit regulation in epilepsy animal models. It has been demonstrated that the levels of this factor is found to increase after prolonged seizures and also after the actions of neurosteroids are withdrawn[27].

DIAGNOSIS

Catamenial epilepsy may be diagnosed by the evaluation of menstrual cycle and the seizure reporting diaries, by characterising the cycle type and duration. Few epileptic women have excessive risk of dysfunction of ovaries. In a recent study 25% of epileptic women with generalized seizures were found to have anovulatory cycles compared to women with focal seizures . so the generalised seizures may be considered as predictor for ovarian dysfuction which could cause failure of ovulation. In another similar study, about 40 women out of 100 epileptic women showed anovulatory cycles. Analysing multiple successive menstrual cycles is mandatory to assess the occurrence of anovulatory cycle. This study proved

the seizure clusters more frequently occurring with women having anovulatory cycles[28].

The best way to assess if there is worsening of seizures during certain phases of menstrual cycle is to have the patient maintain a note of the seizure clusters in relation to her menstrual cycle. Taking the first day of menstrual bleeding as the first day of the menstrual cycle, it is divided into four phases:

1. Menstrual phase – days -3to 3
2. Follicular phase – days 4 to 9
3. Ovulatory phase – days 10 to 16
4. Luteal phase – days 17 to -3

In each phase of the cycle, the frequency of seizures is assessed. The mean number of seizure episodes in each part of the cycle is assessed and compared to that during other parts of cycle. This aids in classifying to a particular type oof catamenial epilepsy. Most acceptable definition is , " a two fold or greater increase in average daily seizure frequency during the affected part of the cycle in comparison to the remainder of the cycle" (Herzog)

If catamenial epilepsy is diagnosed based on the above definition, further measures in evaluation to plan the treatment is as follows:

1. To look for midluteal serum progesterone levels (on twenty second day of the normal menstrual cycle)
2. In there is perimenstural exacerbation of seizures, trough antiepileptic drug levels to be checked on day 22 when the serum estradiol and progesterone levels are at peak and the AED level should within the therapeutic range.

Low AED levels at this period probably because of increased drug metabolism can be the cause of the perimenstural catamenial epilepsy.

Several studies show that in non-epileptic women too there are minor EEG variations during the menstrual cycle. In 1942, according to Dusser de Barenne and Gibbs, during the menses and ovulation EEG shows slowing of background activity .Other studies showed that there was a decrease in the EEG amplitude during the premenstrual and menstrual phases of the cycle[29].

TREATMENT

The management of catamenial epilepsy may be done by adjusting the medications the patient is already taking, non-hormonal and hormonal

therapy. If the antiepileptic drug levels were proved to be low during the seizure clusters or during particular phases of menstrual cycle , increasing the AED dose or adding another AED often a benzodiazepine around that particular time would be helpful in decreasing the seizure frequency. In the past years, many empirical measures of adjusting the pre-existing AED dose or adding another AED mostly a benzodiazepine had been tried in management of the catamenial exacerbation. But these studies were not randomised or blinded or controlled trials. Aggressive measures like hysterectomy or oophorectomy , hormonal manipulation by giving hormone containing contraceptive pills , naturally occurring progesterone and clomiphene have been tried. Other treatment strategies include adding acetazolamide to the AED during the perimenstural period.

Actually there is no particular drug therapy for catamenial epilepsy proven till date as this condition is refractory to many therapies. Among the variety of therapies proposed, adding acetazolamide, benzodiazepines or conventional anticonvulsant drugs with dose adjustment during the particular phases and hormonal therapies are useful. However, the proof for the efficacy of these treatment modalities is still not very clearly established. Multicentre trials may be required to assess the effective treatment for these women with catamenial exacerbation.

NON HORMONAL THERAPY

ACETAZOLAMIDE

Acetazolamide is a potent carbonic anhydrase inhibitor, an important key enzyme for sodium bicarbonate reabsorption and balance of water in the collecting tubules of the kidney. It is also abundantly present in the brain. Acetazolamide is used effectively to control catamenial seizures. It has been demonstrated in a study on twenty epileptic women with different types of generalised and partial epilepsy which showed about thirty to forty percentage of these women had decrease in seizure clusters during the perimenstural period with acetazolamide. The mechanism underlying the action of acetazolamide in catamenial seizures is not clearly understood. But it is evident that after some time tolerance to the drug develops thereby decreasing its efficacy. This may be the reason for administering acetazolamide in a short term basis for the catamenial epilepsy rather than other types of epilepsy.

Acetazolamide is found to be used for many years for the management of catamenial epilepsy. However, the main drawback was the reduction in the efficiency of this drug and development of tolerance to the drug[30].

BENZODIAZEPINES

Benzodiazepines which include clonazepam , clobazam, have allosteric modulating action on GABA A receptor and have wide sprectrum of anticonvulsant property. Clonazepam is commonly used as an add-on drug in absence seizures and myoclonic jerks in children. But the main disadvantage is the tolerance developed by the patients. Clobazam has been widely used for short term in the catamenial seizure, in a dose of 20 - 30mg/kg body weight starting about two to three days prior to day one of menstruation inorder to avoid tolerance development which occurs if given continuously. Other side effects are severe depression and day time sleepiness. The development of tolerance to the drug may be due to long term action of neurosteroids which is observed in animal models. Benzodiazepines may be theoretically utilised for the prophylaxis of catamenial epilepsy. In fact, clobazam which is given for short term is very much useful in the treatment of catamenial seizure exacerbations over long periods of time with satisfying results[31].

HORMONAL TREATMENT

Till date only open controlled analyses of progesterone therapy have been studied. These studies have shown that the treatment with progesterone has considerably reduced the seizure frequency in some women. As the

different patterns of catamenial epilepsy respond in a different manner, the treatment options are complicated.

MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate (MPA) is an oral contraceptive drug that has only progesterone. Zimmerman and colleagues (1973) stated that , MPA has been demonstrated to produce about 30 – 40% decrease in the seizure clusters when studied for about one year. So it is understood that chronic MPA treatment can cause reproductive dysfunction in unpredictable manner. The underlying mechanism of action of MPA is not well established but the progesterone receptors are found to have an infuence in the action of catamenial epilepsy. Contrary to progesterone, MPA is not converted to the neurosteroids and so had no modulating action on GABA A. So, medroxyprogesterone acetate is a better drug than progesterone probably for this particular reason[32].

CYCLIC PROGESTERONE THERAPY

Progesterone has been found to have anticonvulsant properties in women with catamenial epilepsy. It was earlier considered that along with the anticonvulsants progesterone or its metabolites or clomiphene could be used concomitantly. Natural progesterone can be tried in epileptic women with catamenial exacerbation and those with impaired luteal cycles. A

couple of trials where progesterone given as an add on therapy in women with catamenial epilepsy showed significant decrease in the frequency of seizure clusters. Some studies on women with abnormal luteal cycles who also had catamenial epilepsy about six women out of eight showed reduction in seizure frequency with progesterone , about 70% reduction in the seizure frequency . Another open trial where progesterone given as an add on therapy periodically in one group of women and in another group the anticonvulsants alone, there was a 72% of reduction in seizure frequency of generalised seizures and 54% of complex partial seizures in the first group[33].

Progesterone is more useful and the efficacy is greater if given during the second half of the cycle than just during the premenstrual period and then gradually tapered and withdrawn at the end of the menstrual cycle. If progesterone is withdrawn rapidly it can lead on to rebound seizure exacerbation. According to a study by Herzog, "the average daily seizure frequency per patient after 3 years follow up showed that the 15 women who remaind on cyclic progesterone therapy and their original antiepileptic drugs continued to show improved seizure control in comparison to their own baseline. Three women were entirely seizure –free. Four had total seizure reductions of 75 – 99%. Eight had reductions of 50 – 74%. Complex partial seizures in these 15 were lower by a statistically significant 62%,

secondary generalised seizures by 74%. Antiepileptic drug serum levels continued to show no significant change. The three remaining women who continued on progesterone therapy had 10 – 50% improvement at the end of the original investigation at 3 months and were not considered further because they changed antiepileptic drugs" (Herzog)[33]. The drawback of these studies is that the results are also biased by analysing only 15 of the 25 subjects.

The study with transcranial magnetic stimulation analysed that progesterone increases inhibitory effect in the brain during the premenstrual period. Natural progesterone is given thrice daily due to the half-life of about 4 to 6 hours. The usual daily dose range from 300 to 600mg. The dose and the schedule of the drug should be individualised and based on clinical seizure frequency reduction and also serum progesterone levels between 20 – 40 ng/ml. Progesterone is available in another form in capsule preparation that has similar anticonvulsant actions yet it is not fully evident. Theoretically, the progesterone in this form passes though the liver first and cause the delivery of progesterone and its metabolites in different concentrations[33]. Side effects occurring with overdosage are excessive sleepiness, depression and asthenia, tenderness of breast , obesity, menorrhagia. The dose of anticonvulsants need to be increased as progesterone might increase the liver metabolism and protein binding of the

anticonvulsants especially phenobarbitone, carbamazepine and. The use of progesterone associated with the anticonvulsant drug level changes has been sporadic and not in a predictable way. So the free AED level in serum needs to be measured regularly while the patient on progesterone[34].

NEUROSTEROIDS

Although there are several forms of catamenial epilepsy, neurosteroids have been implicated only in the seizure exacerbations that occur in the most common situation, which is when women with normal menstrual cycles experience seizure exacerbations in the perimenstrual period. The neurosteroid withdrawal model of catamenial epilepsy was used to investigate therapies for perimenstrual catamenial epilepsy. A key result is that conventional antiepileptic drugs, including benzodiazepines and valproate, have reduced potency in protecting against seizures during the period of enhanced seizure susceptibility following neurosteroids withdrawal. This pharmacoresistance seems to mimic the situation in women with catamenial epilepsy where breakthrough seizures occur despite treatment with antiepileptic drugs. In contrast to the results with conventional antiepileptic drugs, neurosteroids, including allopregnanolone, THDOC and their 5β-isomers, were found to have enhanced activity in the perimenstrual catamenial epilepsy model[35]. This suggested a "neurosteroid replacement" approach to treat catamenial seizure exacerbations. A

neurosteroid could be administered in a “pulse” prior to menstruation and then withdrawn, or continuously administered throughout the month. While intermittent administration at the time of increased seizure vulnerability is rational, continuous administration would avoid withdrawal of the therapeutic agent, which itself could predispose to seizures[36]. The neurosteroid would be administered at low doses to avoid sedative side effects. Such low doses are expected to contribute little anticonvulsant activity during most of the menstrual cycle. Patients would still require treatment with conventional antiepileptic medications. However, during the period of enhanced seizure susceptibility at the time of menstruation, the increased potency of the neurosteroid would confer protection against perimenstrual seizure exacerbations. It is noteworthy that while the anticonvulsant activity of neurosteroids increases in conjunction with neurosteroid withdrawal, there is no corresponding increase in side effects (mainly sedation), at least as assessed by a measure of motor impairment. Therefore, enhanced side effects, which would negate the potential of the therapeutic approach, would not be expected to occur[36].

GANAXOLONE

Ganaxolone is a neuroactive steroid that modulates the GABA A receptor complex. It is also a potent synthetic analogue of allopregnanolone and is currently under trial. A moderate improvement in seizures was

achieved in women with perimenstural seizures treated with ganaxolone 300mg twice daily from day 21 of the cycle through day 3 of menses (McAuley et al. 2001)[37]. To determine whether the enhanced activity of neurosteroids is due to pharmacokinetic or pharmacodynamic factors, brain and plasma levels of the neurosteroid ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) were determined with a liquid chromatography-mass spectrometric method. Control and neurosteroid withdrawn animals received a single dose of ganaxolone (7 mg/kg, subcutaneously), resulting in an elevation in PTZ threshold that peaked at 30 min and returned to baseline at 120–180 min. Ganaxolone caused a markedly greater (1.8-fold) elevation of PTZ threshold in the withdrawn animals than in controls, indicating a greater sensitivity to the anticonvulsant effects of ganaxolone. Surprisingly, plasma and brain ganaxolone levels were reduced in withdrawn animals (69% of control levels). Adjusting for the reduced brain levels, the pharmacodynamic sensitivity to ganaxolone was enhanced 2.3-fold in the withdrawn animals compared with controls. There was a significant increase in clearance (CL) of ganaxolone in the withdrawn animals, which accounts for the reduced plasma and brain levels. Brain levels of ganaxolone reached a peak more slowly (Tmax-brain, ~30 min) than in plasma (Tmax-plasma, ~15 min); the Tmax-brain value corresponds with the peak elevation in seizure threshold. These studies confirmed the enhanced anticonvulsant

activity of ganaxolone in the rat model of catamenial epilepsy[35]. The enhanced activity occurs in the face of decreased plasma and brain ganaxolone levels, indicating a marked increase in pharmacodynamic sensitivity. Ganaxolone might be effective in treating catamenial epilepsy due to fewer side effects as compared to other hormonal side effects. According to a multicentre clinical trial done by Laxer et al demonstrated the side effects of ganaxolone were less and ganaxolone was tolerated as placebo in women with catamenial epilepsy[38]. Moreover, neurosteroid withdrawal causes markedly greater seizure provocation in the catamenial epilepsy model, consistent with earlier studies demonstrating enhanced seizure susceptibility in acute seizure models. In catamenial epilepsy, breakthrough seizures occur despite treatment with antiepileptic drugs. Previous studies and the new results from Lawrence et al. support the potential of neurosteroids as a novel treatment approach for these pharmacoresistant seizures[39]. Although neurosteroids seems to be the most direct approach to the treatment of catamenial epilepsy, there is only limited anecdotal data available to support their use. No neurosteroids is currently approved. In contrast, there is considerable support from human clinical trials for the use of adjunctive progesterone in the treatment of perimenstrual catamenial epilepsy. It is recommended that the hormone be administered during the entire second half of the menstrual cycle and

tapered gradually as it is believed that abrupt discontinuation can result in rebound seizure exacerbation. Enthusiasm for the use of progesterone in the treatment of catamenial epilepsy had been tempered by the lack of data from adequately controlled clinical trials.

Neurosteroids, such as ganaxolone, have not been associated with such side effects and may ultimately prove to be superior as a treatment approach. In the treatment regimen used in the clinical trials, progesterone is administered only after cycle day 14 and is tapered and discontinued during days 26 to 28 as it is believed that starting earlier than mid-cycle would interfere with normal cycling and lead to irregular bleeding. An advantage of hormonally-inactive neurosteroids is that they can be administered throughout the cycle, simplifying the treatment regimen. New oral preparations of ganaxolone with better bioavailability are under study.

Materials and Methods

MATERIALS AND METHODS

INCLUSION CRITERIA

All women who have attained menarche attending Epilepsy clinic in our institution with recurrent seizures and taking more than one primary anticonvulsant

EXCLUSION CRITERIA

1. Women who are yet to attain menarche and who had attained menopause
2. Women who are seizure free for more than one year
3. Seizures with an underlying cause
4. Women who take single anticonvulsant

STUDY POPULATION

100 women with recurrent seizures attending epilepsy clinic who have been selected based on our inclusion and exclusion criteria

STUDY PERIOD

6 months (January 2013 to june 2013)

METHOD

All the women included in the study were asked to maintain a diary of menstrual cycle, to note down the first day and last day of the menstrual

period. They were also asked to note the date and time of occurrence of the seizure episode.

The clusters of seizure occurrence were noted and its relation with respect to the phases of menstrual cycle documented. On the midluteal phase (day 21) of the menstrual cycle, Serum estradiol and progesterone levels were done in women with catamenial epilepsy done and compared with that of their age matched non-catamenial women.

With the results, the prevalence of catamenial epilepsy among the women with recurrent seizures in the reproductive age group will be identified and they are categorised into subtypes of catamenial epilepsy.

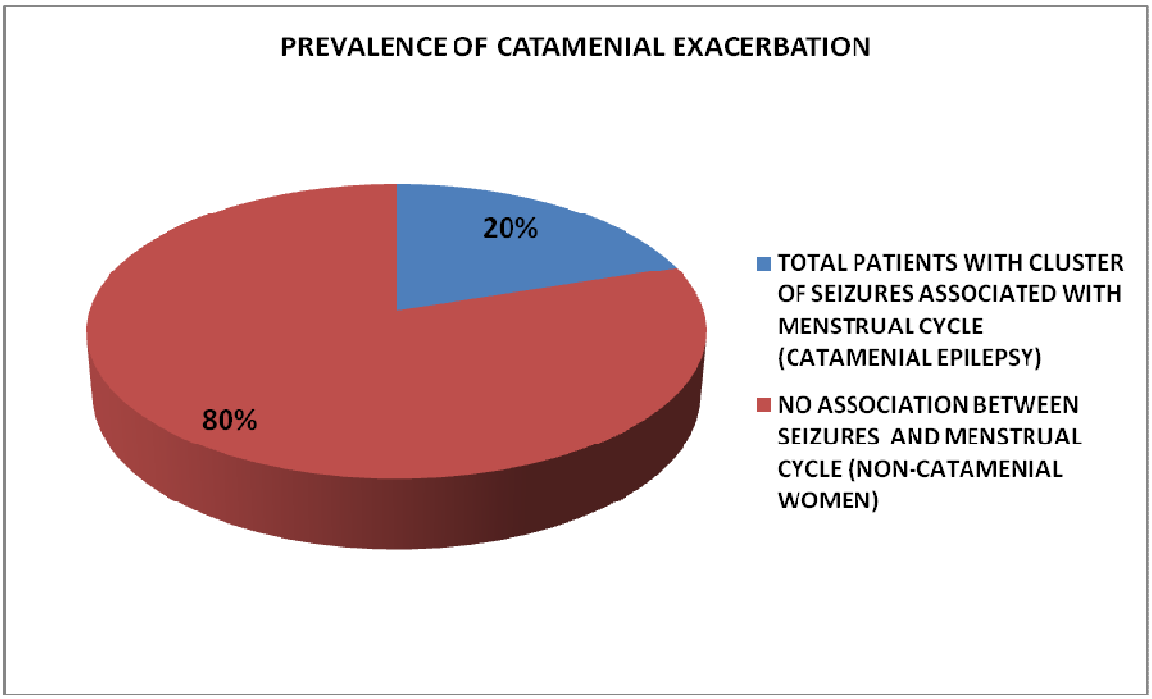
Observation and Results

OBSERVATION AND RESULTS

The total number of women with recurrent and refractory seizures – 100
N = 100

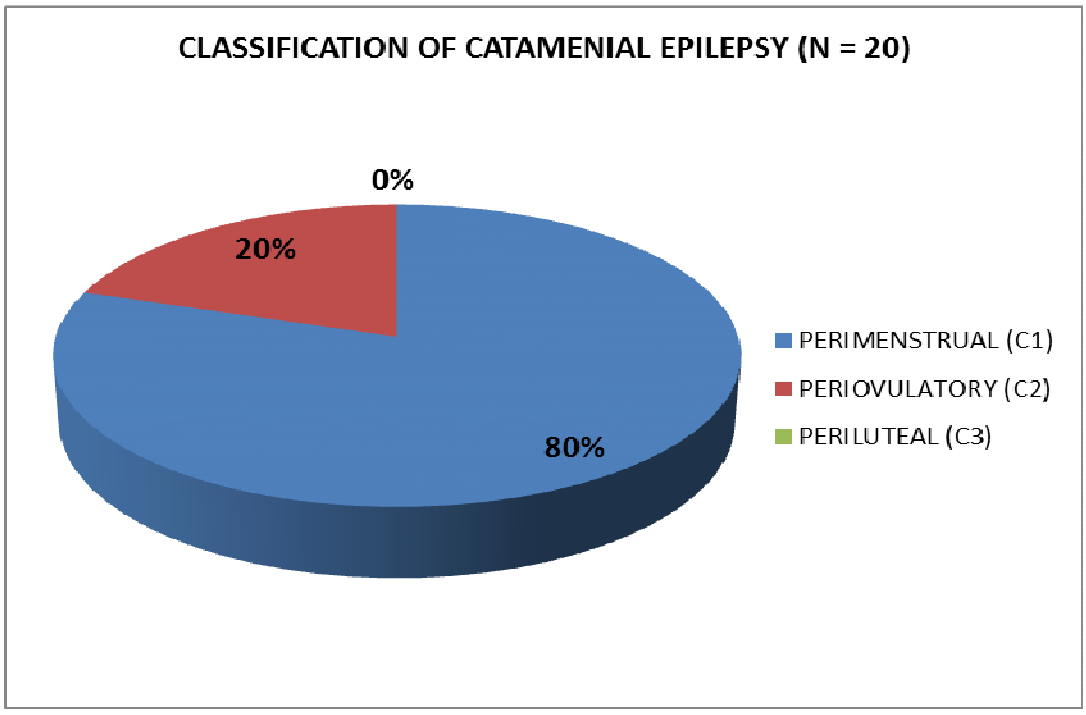
PREVALENCE OF CATAMENIAL EXACERBATION

Total patients with cluster of seizures associated with menstrual cycle (Catamenial Epilepsy)	20
No association between seizures and menstrual cycle (Non-Catamenial women)	80



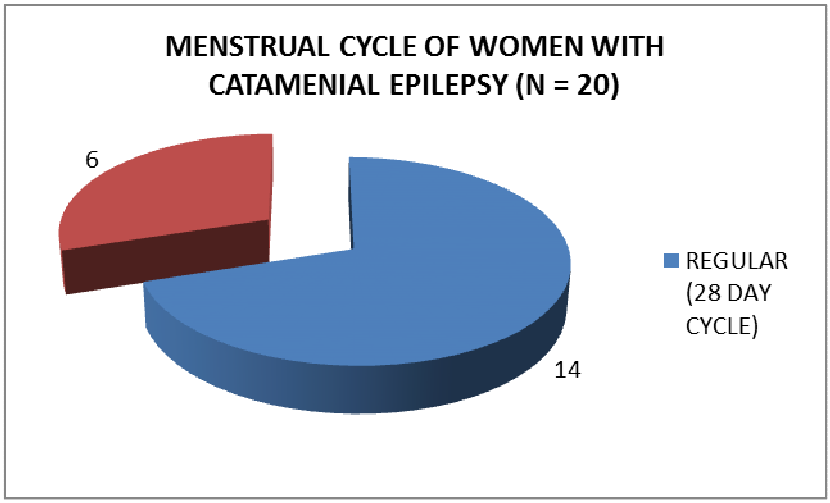
CLASSIFICATION OF CATAMENIAL EPILEPSY (N = 20)

TYPE	NUMBER	PERCENTAGE
PERIMENSTRUAL (C1)	16	80
PERIOVULATORY (C2)	4	20
PERILUTEAL (C3)	0	0



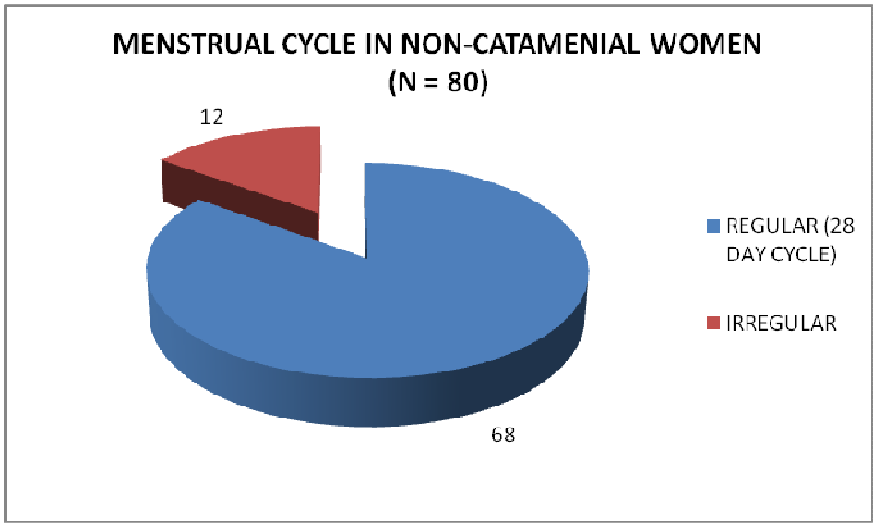
MENSTRUAL CYCLE OF WOMEN WITH CATAMENIAL EPILEPSY (N = 20)

REGULAR (28 DAY CYCLE)	IRREGULAR
14 (70%)	6 (30)



MENSTRUAL CYCLE IN NON-CATAMENIAL WOMEN (N = 80)

REGULAR (28 DAY CYCLE)	IRREGULAR
68 (85%)	12 (15%)



SERUM ESTRADIOL (pg/ml) AND PROGESTERONE LEVELS (ng/ml) ON MID-LUTEAL (DAY 21) OF 28 DAY MENSTRUAL CYCLE IN WOMEN WITH CATAMENIAL EPILEPSY AND NON-CATAMENIAL EPILEPSY

Sl. No.	CATAMENIAL			NON-CATAMENIAL		
	Age (yrs)	Estradiol (pg/ml)	Progesterone (ng/ml)	Age (yrs)	Estradiol (pg/ml)	Progesterone (ng/ml)
1	25	160	8.97	26	137	14.33
2	27	253	9.24	27	135	14.25
3	19	263	8.07	18	132	14.23
4	18	196	10.09	19	174	16.69
5	32	328	8.38	30	139	14.55
6	35	181	6.32	35	184	12.15
7	28	330	8.62	28	130	16.64
8	23	323	8.60	24	175	16.09
Mean ± SEM	25.87 ± 5.91	254.25*** ± 69.30	8.53*** ± 1.08	26.625 ± 5.476	150.75 ± 22.65	14.86 ± 1.53

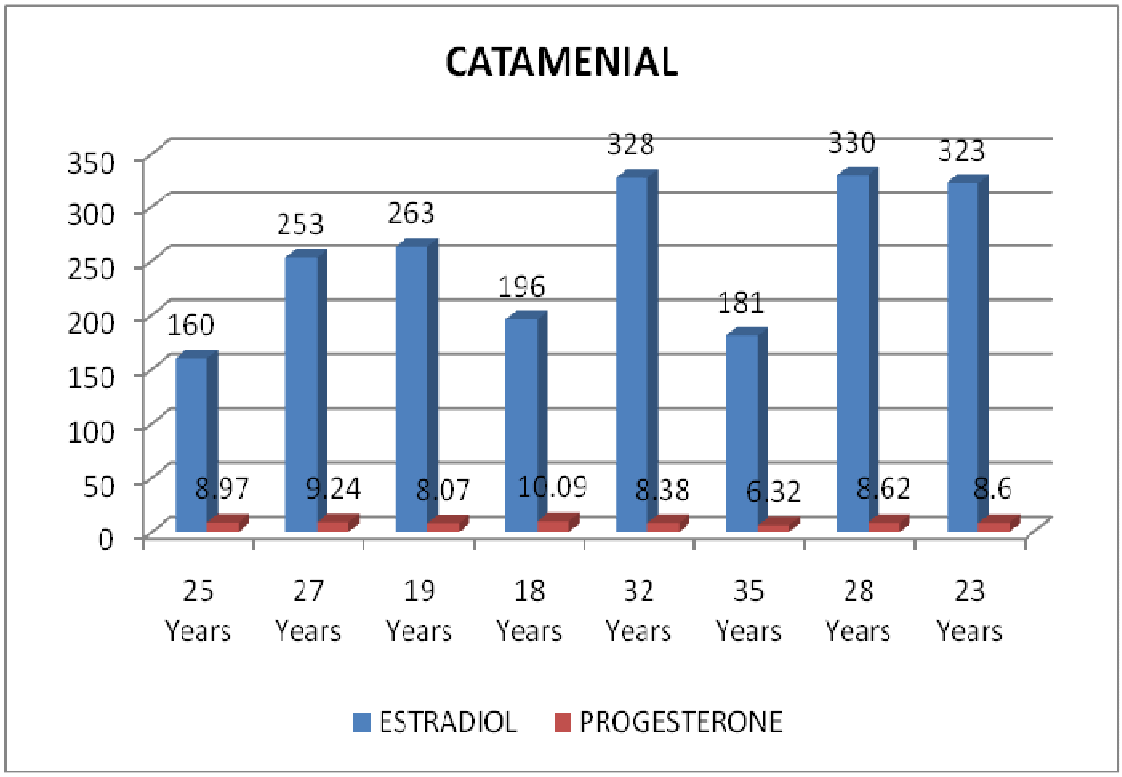
*** P<0.001, pg-Picogram & ng-Nanogram

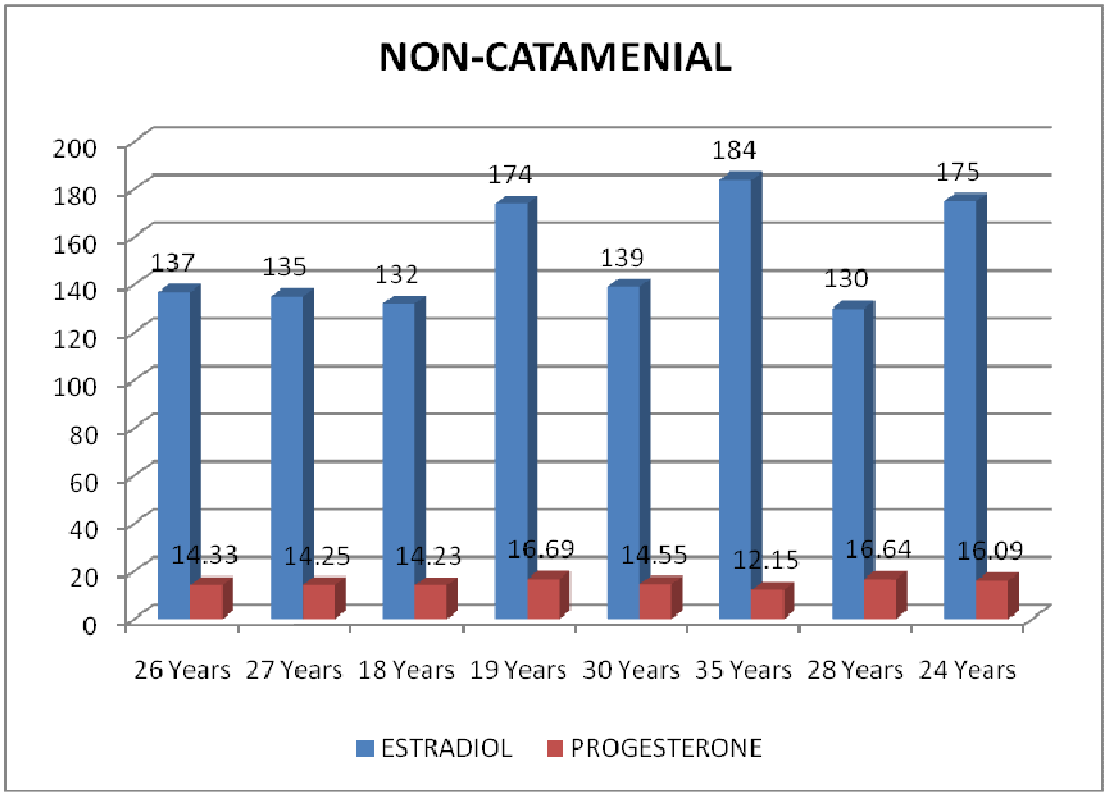
(Luteal phase normal values: Estradiol - 43.8-211 pg/ml & Progesterone - 1.7-27 ng/ml)

Statistics

Statistical analysis was performed with Graph Pad statistical software package version 3.05 (GraphPad Software, Inc , San Diego, California).Hormonal data were analysed using one-way ANOVA with Tukey Post test, Values are presented as Mean ± SEM, and p value of < 0.05 was considered statistically significant.

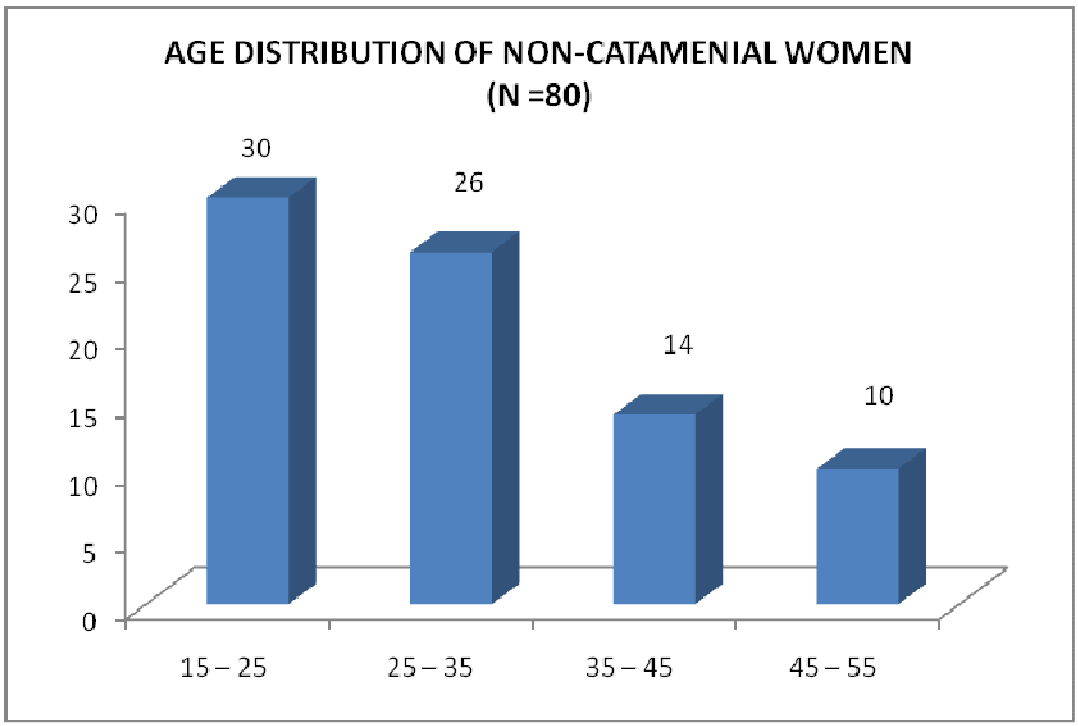
HORMONE LEVELS





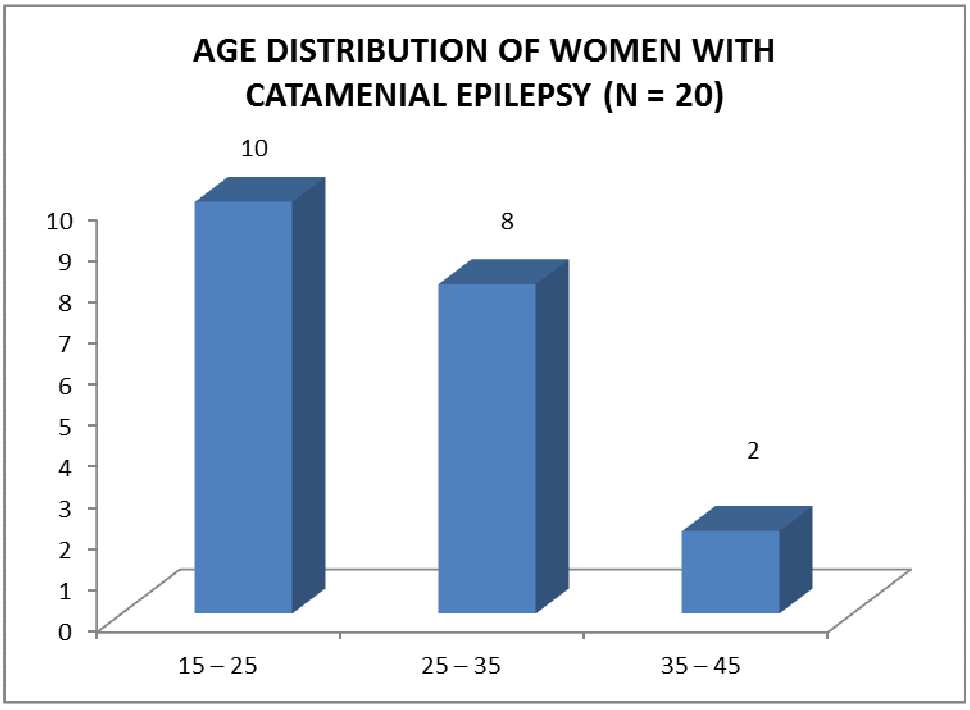
AGE DISTRIBUTION OF NON-CATAMENIAL WOMEN (N =80)

AGE (YEARS)	TOTAL NUMBER	PERCENTAGE
15 – 25	30	37.5
25 – 35	26	32.5
35 – 45	14	17.5
45 – 55	10	12.5



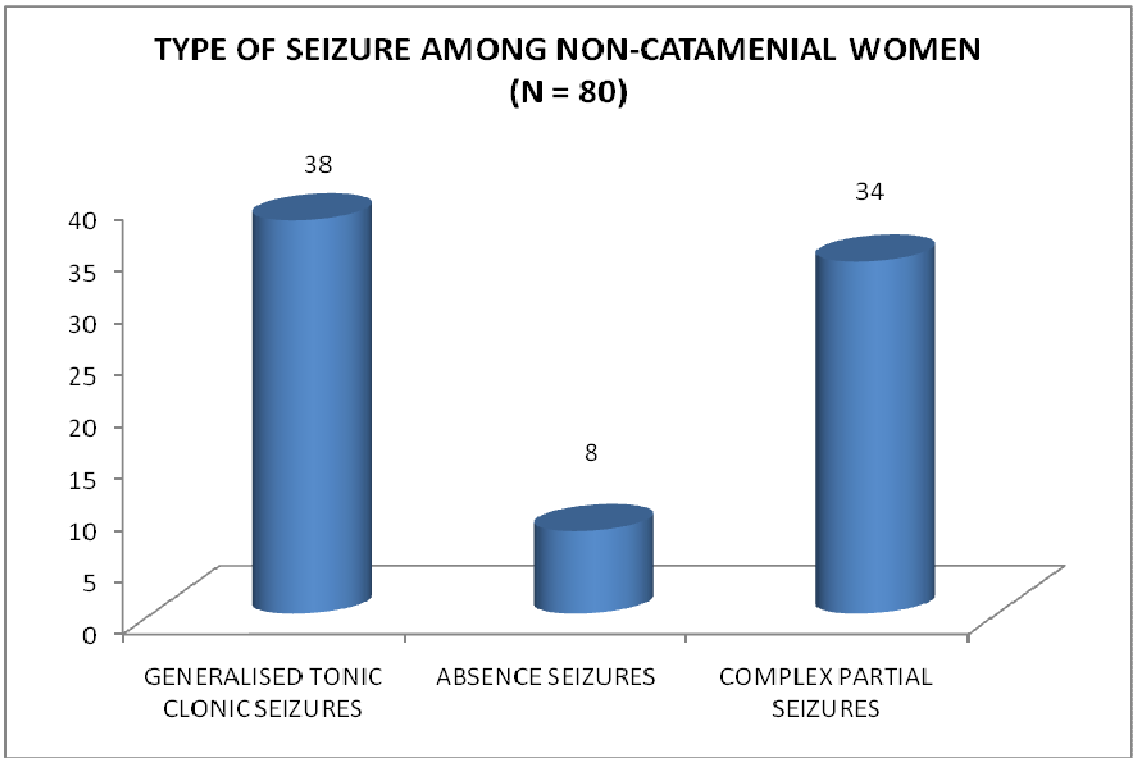
AGE DISTRIBUTION OF WOMEN WITH CATAMENIAL EPILEPSY (N = 20)

AGE GROUP	NUMBER	PERCENTAGE
15 – 25	10	50
25 – 35	8	40
35 – 45	2	10



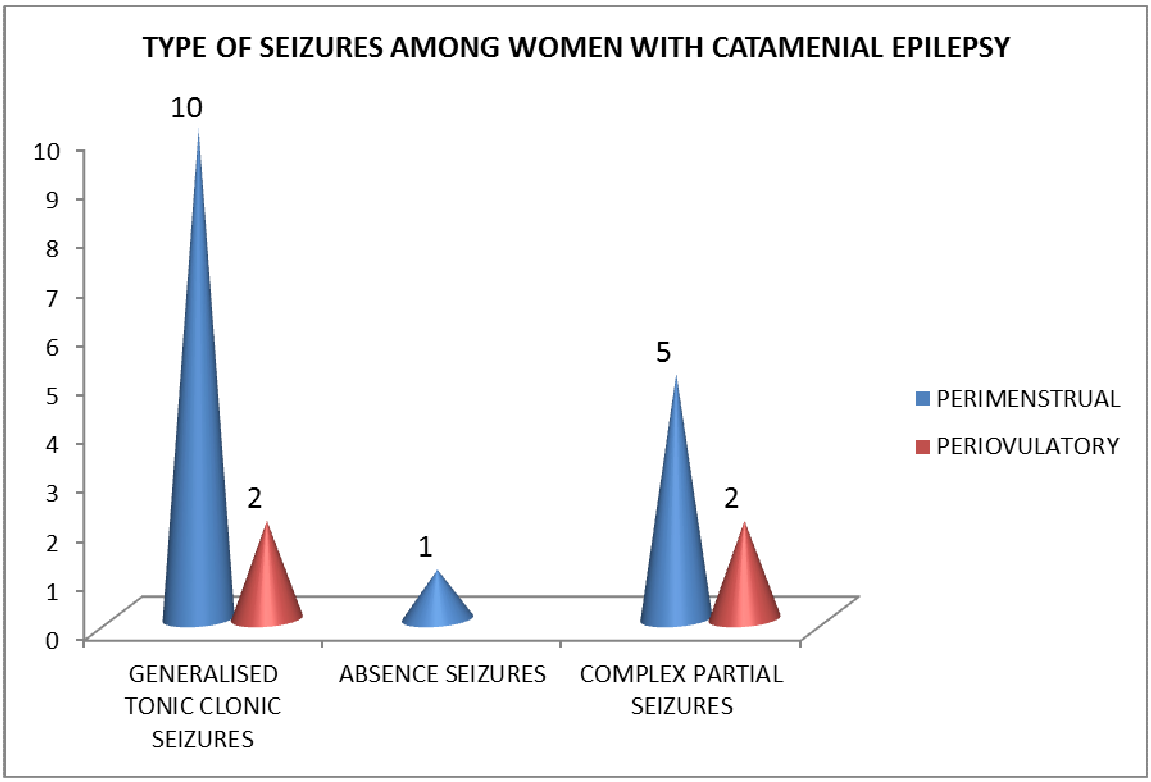
TYPE OF SEIZURE AMONG NON CATAMENIAL WOMEN
(N = 80)

TYPE OF SEIZURE	NUMBER	PERCENTAGE
Generalised Tonic Clonic Seizures	38	47.5
Absence Seizures	8	10
Complex Partial Seizures	34	42.5



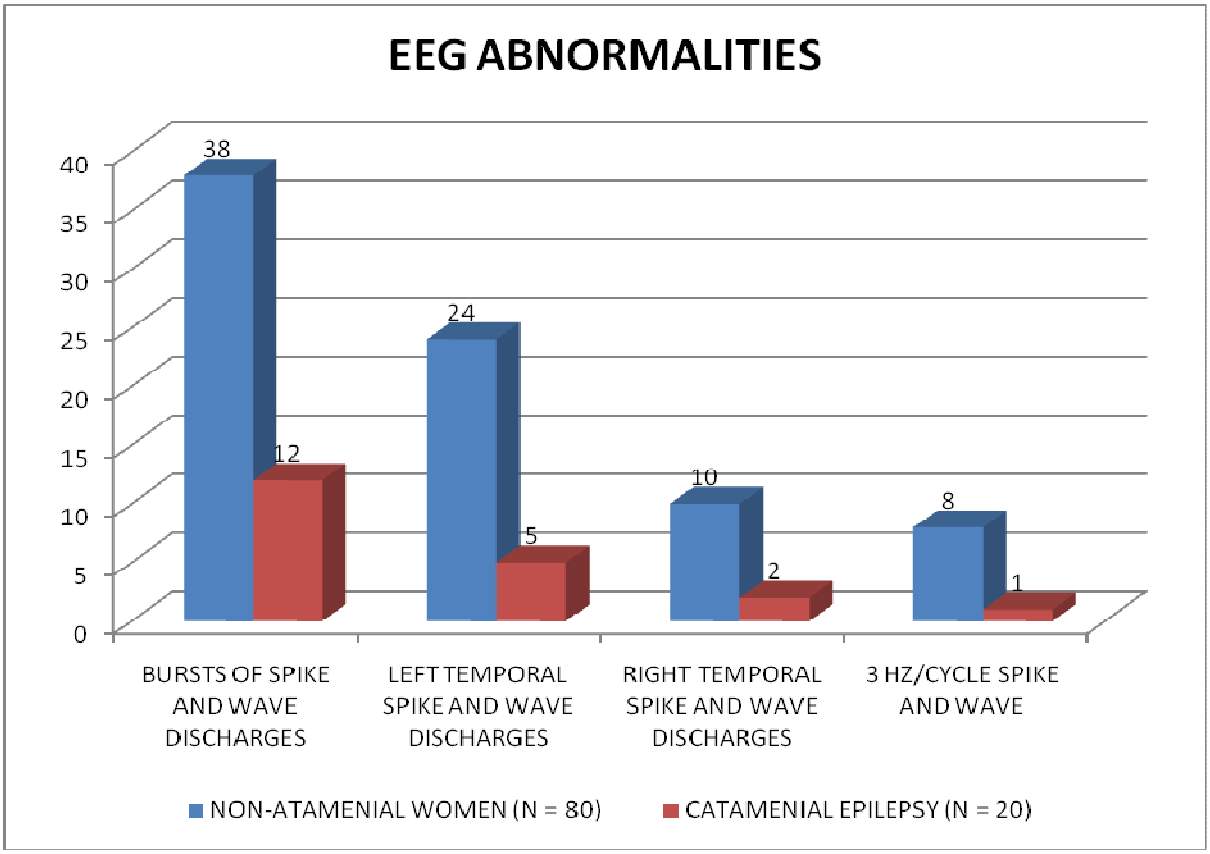
TYPE OF SEIZURES AMONG WOMEN WITH CATAMENIAL EPILEPSY

TYPE OF SEIZURES	PERIMENSTRUAL (16)	PERIOVULATORY (4)
Generalised Tonic Clonic Seizures	10 (62.5%)	2 (50%)
Absence Seizures	1 (6.25%)	-
Complex Partial Seizures	5 (31.25%)	2 (50%)



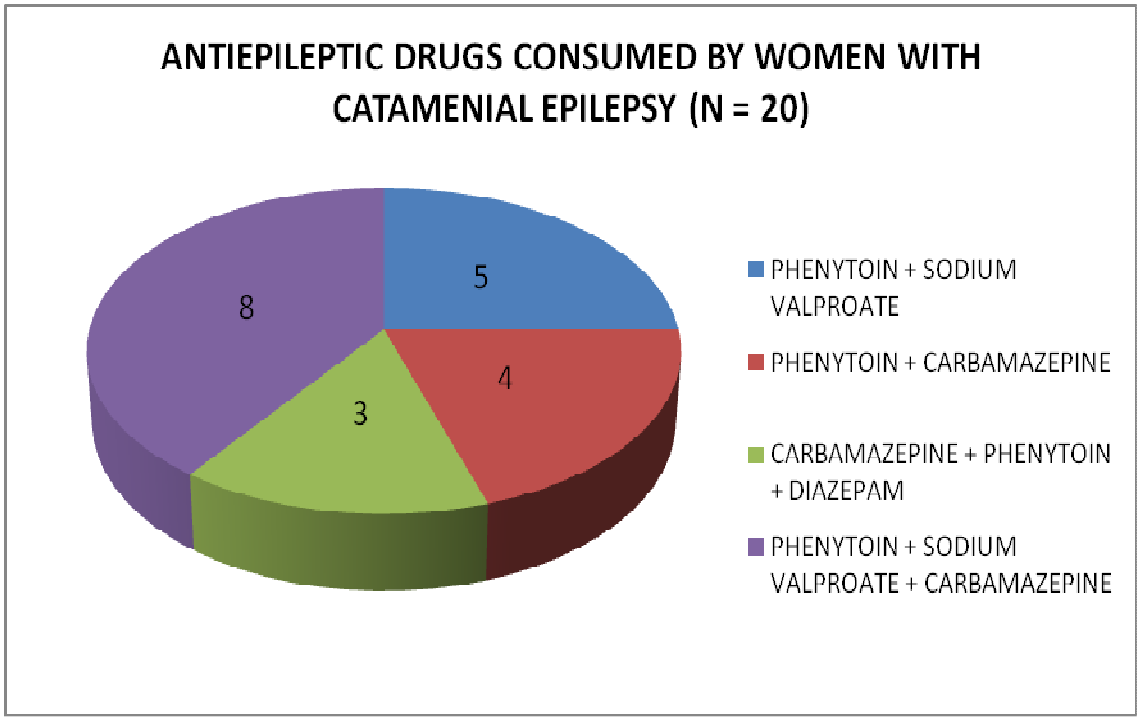
EEG ABNORMALITIES

EEG FINDINGS	NON-CATAMENIAL WOMEN (N = 80)	CATAMENIAL WOMEN (N = 20)
Bursts of spike and wave discharges	38 (47.5%)	12 (60%)
Left temporal spike and wave discharges	24 (30%)	5 (25%)
Right temporal spike and wave discharges	10 (12.5%)	2 (10%)
3 hz/cycle spike and wave	8 (10%)	1 (5%)



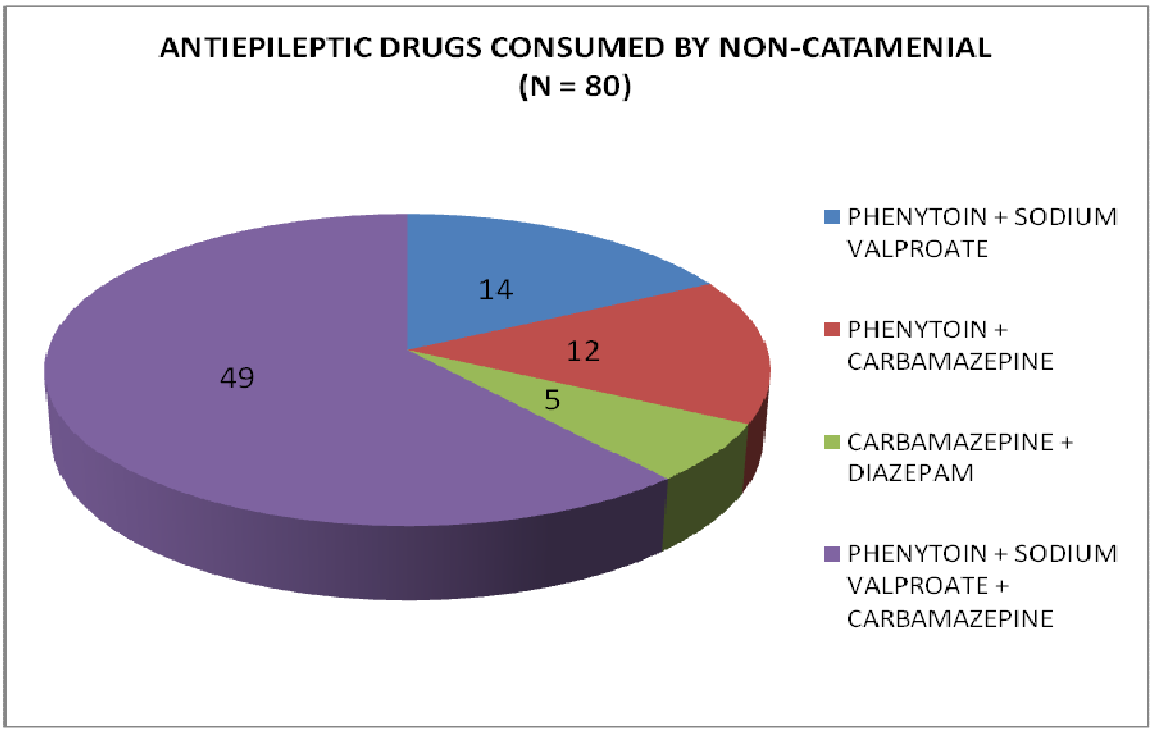
ANTIEPILEPTIC DRUGS CONSUMED BY WOMEN WITH CATAMENIAL EPILEPSY (N = 20)

Phenytoin + Sodium Valproate	5 (25%)
Phenytoin + Carbamazepine	4 (20%)
Carbamazepine + Phenytoin + Diazepam	3 (15%)
Phenytoin + Sodium Valproate + Carbamazepine	8 (40%)



ANTIEPILEPTIC DRUGS CONSUMED BY NON-CATAMENIAL WOMEN (N = 80)

Phenytoin + Sodium Valproate	14 (17.5%)
Phenytoin + Carbamazepine	12 (15%)
Carbamazepine +Phenytoin + Diazepam	5 (6.25%)
Phenytoin + Sodium Valproate + Carbamazepine	49 (61.25%)



Discussion

DISCUSSION

Catamenial epilepsy is one of the rare subtypes of epilepsy that occurs specially in women with epilepsy who have exacerbation of seizures around specific phases of menstrual cycle. There is a wide variation in prevalence of catamenial epilepsy as there are no clear criteria to define or diagnose this condition. During recent times with increasing awareness regarding the influence of hormones on the neuronal excitability, many studies have been done to understand this rare condition.

Out of 100 women with recurrent seizures, 20 showed catamenial pattern of seizure occurrence. These 20 women had seizure clusters occurring periodically at a particular phase of menstrual cycle as assessed by the seizure –menses diary for six consecutive months. So the prevalence of catamenial epilepsy according to our study is 20%. This percentage of catamenial pattern as observed in our study is less compared to other recent studies. Herzog et al, (2004) in his study showed that 39% had catamenial epilepsy. He analysed 89 women with epilepsy who charted their menstrual period and seizures for three cycles[40]. In a more recent study by El Khayat et al, (2008), about 31% of epileptic women showed catamenial seizures[23]. One study done by Duncan et al, showed the prevalence rate of 12.5%

which is much less compared to our study[41]. Bhazan et al (2005) and Reddy et al, (2004) showed that the prevalence of catamenial epilepsy was quite a wide range from 10 – 70%[15]. This wide range and disparity of prevalence of catamenial seizures in various studies is probably due to absence of a precise definition or criteria to define the pattern and absence of a uniform methodology in selecting the patients and analysing the seizure cluster pattern in relation to various stages of menstrual cycle. There is no consensus on analysing the pattern of catamenial seizure occurrence. Another reason is that the study population in all these studies represent the selected population and the results cannot be generalised for the entire population of epileptic women.

Among the 20 women with catamenial epilepsy, 16 (80%) had perimenstrual type of catamenial epilepsy, 4 (20%) had periovulatory type. None of the epileptic women in our study had the third type which is the luteal type of catamenial epilepsy. This classification was done based on the distinct patterns of catamenial epilepsy as explained by Herzog et al (1997). In his study, 59% of women with catamenial epilepsy were under the perimenstural category and he concluded this type as the commonest of the other types of catamenial epilepsy[14]. Another study by El Khayat et al (2008) also showed similar results. Thus several studies done on the classification of catamenial epilepsy reveal that the commonest of the three

types is the perimenstrual (C1) type and next is periovulatory (C2) type. Both these types occur in women with ovulatory menstrual cycle. Luteal type (C3) is very rare and is found in anovulatory cycles. Herzog et al (2008) showed in his study that 16.5% of women with catamenial epilepsy had anovulatory cycles and had luteal type of catamenial epilepsy[42]. Our study also showed the Perimenstrual type as the most predominant among other types of catamenial epilepsy similar to other studies. We did not fine the occurrence of third type the periluteal type of catamenial epilepsy among our study population. The third type as such is a rare entity and that could be the reason.

Out of the 20 women with catamenial epilepsy, 14 (70%) had regular 28 day menstrual cycle and the remaining 6 (30%) had irregular menstrual cycle. The women with irregular menstrual cycle also had perimenstural type of catamenial epilepsy. In the 80 women in noncatamenial group, 68 (85%) had regular cycle and 12 (15%) had irregular cycles. There was no correlation observed in our study regarding the regularity of the menstrual cycle and the prevalence or type of catamenial epilepsy. Detailed background hormonal and gynaecological analysis is required in a bigger population to comment on the menstrual cycle periodicity which could have an influence over the type of catamenial epilepsy.

On day 21 of menstrual cycle, serum estradiol and progesterone levels were analysed in eight women with catamenial epilepsy who had regular 28 day menstrual cycle and their age matched controls in the non-catamenial group. There was statistically significant increase in the level of serum estradiol in the women with catamenial epilepsy compared to the noncatamenial group. The progesterone level was significantly low in the group of catamenial epilepsy than in the women with the non-catamenial epilepsy. Both serum estradiol and progesterone levels are expected to be at the baseline during the 21st and 22nd day of the cycle in a regular 28 day menstrual cycle. This period corresponds to the mid-luteal phase of the menstrual cycle. The increase in the oestrogen level which has proconvulsant properties and withdrawal of progesterone with anticonvulsant properties might support the pathophysiology of catamenial epilepsy. Studies done by Herzog et al (1997) and Backstrom (1976) showed similar results suggesting the excess estradiol or withdrawal of progesterone contribute to catamenial epilepsy[43]. In a study done by Zahir Hussain (2006) proved statistically significant increase in the level of estradiol among catamenial women compared to the age matched non-catamenial women[44].

Among the women in the noncatamenial group, out of 80, 30 (37.5%) were in the age group of 15 -25 years, 26 (32.5%) were within the range of

25 – 35 years, 14(17.5%) were in the group of 35 – 45 years and 10 (12.5%) women were in the range of 45 – 55 years. In the catamenial group, out of 20, 10 (50%) were in the age group of 15 – 25 years, 8(45%) were in the group of 25 – 35 years and 2 women (10%) were in the group of 35 – 45 years. Majority of women with catamenial epilepsy were in the age group of 15 – 25 years which is the active reproductive period during which there are major fluctuations in the gonadal hormones. There was no major difference in the age distribution of the women in the noncatamenial group however slight preponderance was observed in the age group of 15 – 25 years.

In the catamenial epilepsy group, among the women with perimenstrual type, 10 (62.5%) had generalised tonic clonic seizures, 5 (31.25%) had complex partial seizures and 1(6.25%) had absence seizure. Among the women with periovulatory type of catamenial epilepsy, 2 (50%) had generalised tonic clonic seizures and 2 (50%) had complex partial seizures. There was no specific type of seizure semiology or seizure syndrome associated with catamenial epilepsy noted in our study.

All the women included in our study were on more than one primary anticonvulsant. Phenytoin and sodium valproate were taken by 14 (17.5%) of women in non-catamenial group and 5 (25%) of women in catamenial

group. Pheynytoin and carbamazepine were taken by 12 (15%) in the non-catamenial group and 4 (20%) in catamenial group. 49 (61.25%) of women in non-catamenial group and 8 (40%) women with catamenial epilepsy were on phenytoin, carbamazepine and sodium valproate. 3 women in catamenial epilepsy group were on carbamazepine and phenytoin with intermittent diazepam but continued to have cyclic seizure exacerbation.

Conclusion

CONCLUSION

The following are the observations of our study:

1. Catamenial epilepsy was observed in 20% of women with recurrent and refractory seizures attending the epilepsy clinic in our institution.
2. The perimenstrual type (C1) was the commonest among the women with catamenial epilepsy.
3. The catamenial epilepsy was commonly found in the age group of 15 to 25 years in our study.
4. There was significant increase in the level of serum estradiol level and decrease in the level of progesterone among women with catamenial epilepsy compared to noncatamenial group.
5. Majority of women with catamenial epilepsy in our study had generalised tonic clonic seizures and no specific seizure type confined to any particular type of catamenial epilepsy.

A wide population of women with epilepsy are treated with multiple anticonvulsants and are considered refractory to treatment. The under recognition and lack of awareness of catamenial epilepsy could be one of the reasons behind the polytherapy of anticonvulsants in many such women, especially in our country. There are very few studies analysing the prevalence of catamenial epilepsy in our country. Among the women with

pharmacoresistant epilepsy, about one fifth of women according to our study fall under the category of catamenial epilepsy where the appropriate treatment strategy would reduce the burden in the lives of these epileptic women.

Our study proposes following recommendations:

1. All epileptic women of childbearing age could be educated to maintain an accurate seizure and menstrual diary in order to identify and manage the catamenial epilepsy.
2. It is important to do a precise hormonal analysis in appropriate phases of menstrual cycle in women with catamenial epilepsy.
3. It is also essential to do antiepileptic drug level during the cluster of seizures in order to analyse the influence of the gonadal hormones on the anticonvulsant drug metabolism during various phases of menstrual cycle.

Thus, the recognition and appropriate management of catamenial epilepsy in women with refractory epilepsy would be an ideal solution in reducing the seizure clusters and improving their quality of life.

Appendix

BIBLIOGRAPHY

1. Tempkin O. The falling sickness: a history of epilepsy from the Greeks to the beginnings of modern neurology. Baltimore: Johns Hopkins Press, 1945.
2. Locock C. Discussion. In: Sieveking EH, ed. Analysis of fifty-two cases of epilepsy observed by the author. Med Times Gaz 1857; 14: 524–526.
3. Gowers WR. Epilepsy and other chronic convulsive diseases. Their causes, symptoms, and treatment. London: J & A Churchill, 1881: 197
4. Smith MJ, Keel JC, Greenberg BD, et al. Menstrual cycle effects on cortical excitability. Neurology . 1999; 53: 2069–2072.
5. Rosciszewska D, Buntner B, Guz I, Zawisza L. Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy. J Neurol NeurosurgPsychiatry . 1986; 49: A47–51. 72.
6. Herzog AG, Klein P, Ransil BJ. Three patterns of catamenialepilepsy. Epilepsia 1997;38:1082—8.
7. Bilo L, Meo R, Nappi C, Annunziato L, Striano S, Colao AM, Mero B, Buscaino GA.Reproductive endocrine disorders in women with primary generalized epilepsy. Epilepsia1988;29:612–19.
8. Logothetis J, Harner R, Morrell F, Torres F. The role ofestrogens in catamenial exacerbation of epilepsy. Neurology (Minneap) 1959;9:352-60.
9. Woolley CS, McEwen BS. Roles of estradiol and progesterone inregulation of hippocampal dendritic spine density during theestrous cycle in the rat. J Comp Neurol 1993;336:293—306.
10. Smith SS. Estrogen administration increases neuronalresponses to excitatory amino acids as a long term effect.Brain Res 1989;503:354—7.
11. Herzog AG. Intermittent progesterone therapy and frequencyof complex partial seizures in women with menstrual disorders. Neurology 1986;36:1607—10.
12. Smith SS, Gong QH, Hau F-C, Markowitz RS, ffrench-Mullen JMH, LiX. GABAA receptor a4 subunit suppression preventswithdrawal properties of an endogenous steroid. Nature1998;392:926—30.

13. Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC. Treatmentof seizures with medroxyprogesterone acetate: preliminaryreport. Neurology (Cleveland) 1984;34:1255—8.

14. Herzog AG, Klein P, Ransil BJ. Three patterns of catamenialepilepsy. Epilepsia 1997;38:1082—8.

15. Reddy, Doodipala S., and Y. C. Zeng. "Effect of neurosteroid withdrawal on spontaneous recurrent seizures in a rat model of catamenial epilepsy." FASEB J 21.885.14 (2007).

16. Herzog AG, Klein P, Ransil BJ. Three patterns of catamenialepilepsy. Epilepsia 1997;38:1082—8.

17. Logothetis J, Harner R. Electrocortical activation by estrogens.Arch Neurol 1960;3:290—7.

18. McEwen BS. How do sex and stress hormones affect nervecells? Ann N Y AcadSci 1994;743:1—16.

19. M Quigg, S D. Smithson, K M. Fowler, T Sursal, A G. Herzog, On behalf of the NIH Progesterone Trial Study GroupNeurology. 2009 July 21; 73(3): 223–227

20. Rosciszewska D. Analysis of seizure dispersion duringmenstrual cycle in women with epilepsy. Monog NeurolSci 1980; 5: 280-284.

21. Teresawa E, Timiras P. Electrical activity during the estrouscycle of the rat; cyclic changes in limbic structures. Endocrinology1968;83:207

22. Logothetis J, Harner R, Morrell F, Torres F. The role ofestrogens in catamenial exacerbation of epilepsy. Neurology(Minneap) 1959;9:352—60.

23. El-Khayat, Hamed A., et al. "Reproductive hormonal changes and catamenial pattern in adolescent females with epilepsy." Epilepsia 49.9 (2008): 1619-1626.

24. Osborne, Danielle M., and Cheryl A. Frye. "Estrogen increases latencies to seizures and levels of 5α-pregnan-3α-ol-20-one in hippocampus of wild-type, but not 5α-reductase knockout, mice." Epilepsy &Behavior 16.3 (2009): 411-414.

25. Herzog AG, Friedman MN, Freund S, Pascual-Leone A. Transcranialmagnetic stimulation evidence of a potential role for progesterone in the modulation of

premenstrual corticocorticalinhibition in a woman with catamenial seizureexacerbation. Epilepsy Behav 2001;2:367—9.

26. Pfaff DW, Keiner M. Estradiol-concentrating cells in the ratamygdala as part of a limbic-hypothalamic hormone-sensitivesystem. In: Eleftheriou B, editor. The neurobiology ofthe amygdala. New York: Plenum Publishing; 1973. p. 775—92.
27. Cheney DL, Uzunov D, Costa E, Guidotti A. Gas chromatographic-mass fragmentographic quantitation of 3a-hydroxy-5a-pragnan-20-one (allopregnanolone) and its precursors inblood and brain of adrenalectomized and castrated rats. JNeurosci 1995;15:4641—50.
28. Bilo, L., Meo, R., 2006. Epilepsy and polycystic ovary syndrome:where is the link? Neurol. Sci. 27, 221—230.
29. Haider, Yasser, and DavidB Barnett. "Catamenial epilepsy and goserelin." The Lancet 338.8781 (1991): 1530.
30. Ansell B, Clarke E. Acetazolamide in treatment of epilepsy. Br Med J 1956;1:650-61.
31. Feely M, Calvert R, Gibson J. Clobazam in catamenial epilepsy: A model forevaluating anticonvulsants. Lancet 1982;2:71-3.
32. Zimmerman AW, Holden KR, Reiter EO, Dekaban AS. Medroxyprogesteroneacetate in the treatment of seizures associated with menstruation. J Pediatr1973;83:959-63.
33. Herzog AG. Progesterone therapy in women with epilepsy: A 3-year follow-up.Neurology 1999;52:1917-8.
34. Herzog AG. Progesterone therapy in women with complex partial and secondarygeneralized seizures. Neurology 1995;45:1660-2.
35. Reddy DS, Rogawski MA. Enhanced anticonvulsant activity of neuroactivesteroids in a rat model of catamenial epilepsy. Epilepsia 2001;337-44.
36. Reddy DS, Woodward R. Ganaxolone: A prospective overview. Drugs Future2004;29:227-42.
37. McAuley JW, Moore JL, Reeves AL, Flyak J, Monaghan EP, Data J. A pilotstudy of the neurosteroidganaxolone in catamenial epilepsy: Clinical experiencein two patients. Epilepsia 2001;42:85.

38. Laxer K, Blum D, Abou-Khalil BW, Morrell MJ, Lee DA, Data JL, Monaghan EP. Assessment of ganaxolone's anticonvulsant activity using a randomized, double-blind, presurgical trial design. GanaxolonePresurgical Study Group. Epilepsia. 2000;41:187–1194.

39. Lawrence C, Martin BS, Sun C, Williamson J, Kapur J. Endogenous neurosteroid synthesis modulates seizure frequency. Ann Neurol. 2010;67:689–693.

40. Herzog, Andrew G., et al. "Frequency of catamenial seizure exacerbation in women with localization-related epilepsy." Annals of neurology 56.3 (2004): 431-434.

41. Duncan, S., Read, C.L., Brodie, M.J., 1993. How common is catamenialepilepsy? Epilepsia 34, 827—831.

42. Herzog, Andrew G. "Catamenial epilepsy: definition, prevalence pathophysiology and treatment." Seizure 17.2 (2008): 151-159.

43. Backstrom T. Epileptic seizures in women related to plasmaestrogen and progesterone during the menstrual cycle. ActaNeurol Scand 1976;54:321—47.

44. Hussain, Zahir, et al. "Influence of steroid hormones in women with mild catamenial epilepsy." J Ayub Med Coll Abbottabad 18.3 (2006).

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CERTIFICATE OF APPROVAL

To
Dr. M. Kavitha,
PG in DM Neurology,
Institute of Neurology,
Madras Medical College, Chennai-3.

Dear Dr. M. Kavitha,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"A study on prevalence of catamenial epilepsy-an elusive condition"** No.22092012

The following members of Ethics Committee were present in the meeting held on 11.09.2012 conducted at Madras Medical College, Chennai-3.

1. Dr. G. Sivakumar, MS FICS FAIS	-- Chairperson
2. Prof. R. Nandini, MD Director, Instt. of Pharmacology, MMC, Ch-3	-- Member Secretary
3. Prof. Shyamraj, MD, Director i/c, Instt. of Biochemistry, MMC, Ch-3	-- Member
4. Prof. P. Karkuzhali, MD Prof. Instt. of Pathology, MMC, Ch-3	-- Member
5. Prof. Kalai Selvi, MD Prof. of Pharmacology, MMC, Ch-3	-- Member
6. Prof. Siva Subramanian, Director, Instt. of Internal Medicine, MMC, Ch-3.	-- Member
7. Thiru. S. Govindasamy, BABL	-- Lawyer
8. Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

20/12/12

Member Secretary, Ethics Committee

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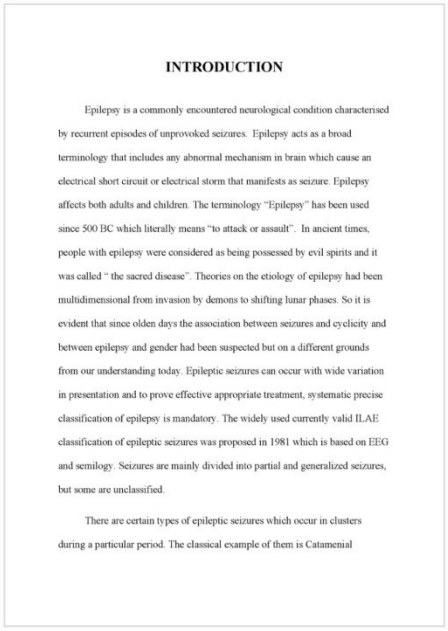
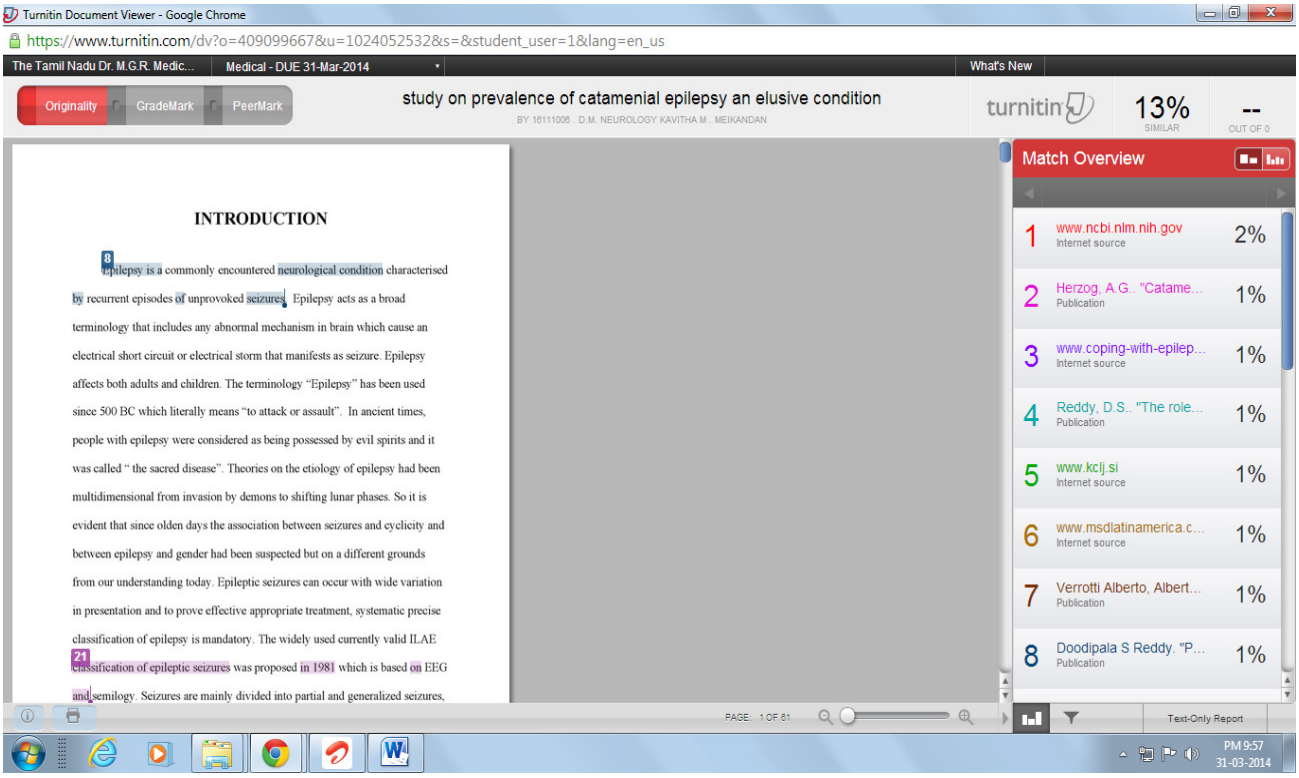


INTRODUCTION

Epilepsy is a commonly encountered neurological condition characterised by recurrent episodes of unprovoked seizures. Epilepsy acts as a broad terminology that includes any abnormal mechanism in brain which cause an electrical short circuit or electrical storm that manifests as seizure. Epilepsy affects both adults and children. The terminology "Epilepsy" has been used since 500 BC which literally means "to attack or assault". In ancient times, people with epilepsy were considered as being possessed by evil spirits and it was called " the sacred disease". Theories on the etiology of epilepsy had been multidimensional from invasion by demons to shifting lunar phases. So it is evident that since olden days the association between seizures and cyclicity and between epilepsy and gender had been suspected but on a different grounds from our understanding today. Epileptic seizures can occur with wide variation in presentation and to prove effective appropriate treatment, systematic precise classification of epilepsy is mandatory. The widely used currently valid ILAE classification of epileptic seizures was proposed in 1981 which is based on EEG and semilogy. Seizures are mainly divided into partial and generalized seizures, but some are unclassified.

There are certain types of epileptic seizures which occur in clusters during a particular period. The classical example of them is Catamenial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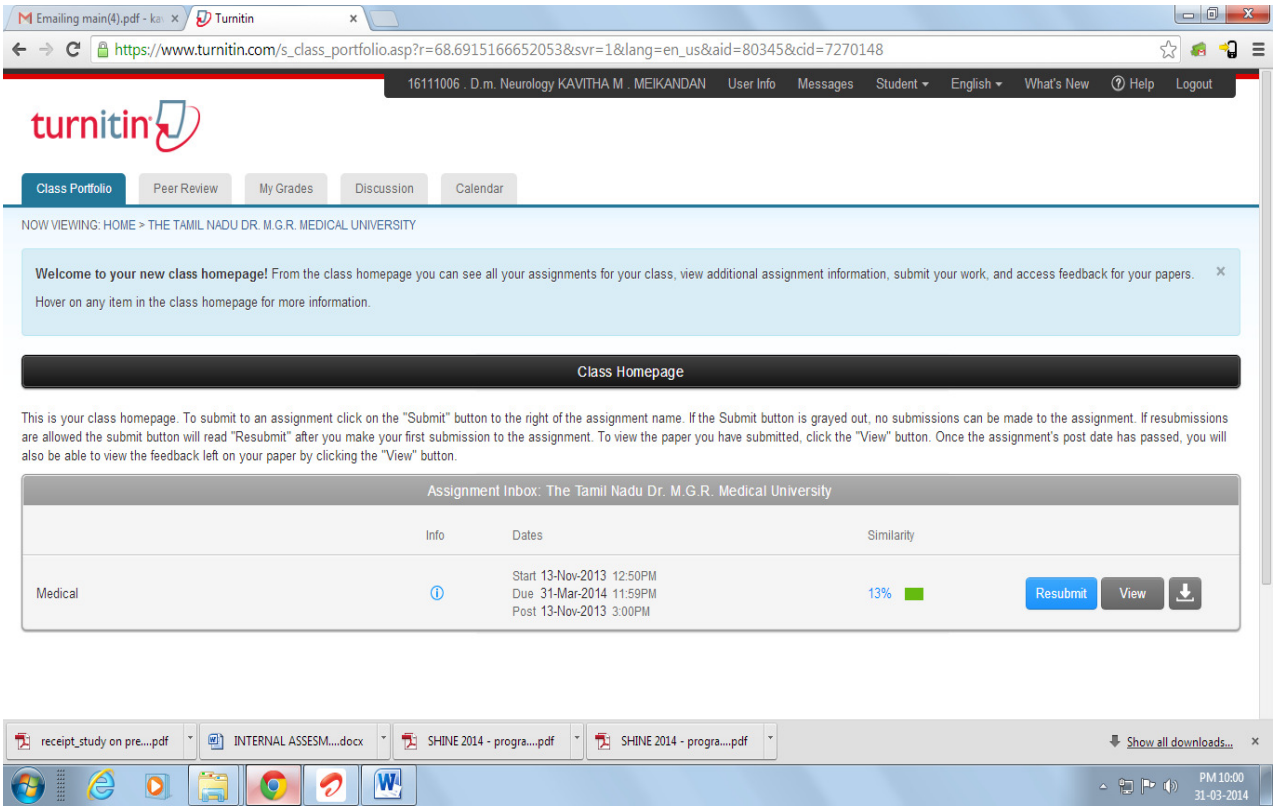
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PROFORMA

Name: Age: MIN no:

Type of Seizure:

Duration of illness:

Frequency:

Any specific precipitating factors:

Anticonvulsant:

Compliance:

Date of Last episode:

First day of last menstrual period:

Last day of last menstrual period:

Menstrual cycle : Regular / Irregular

Premenstrual symptoms:

Marital History:

Details of child birth:

General examination :

Examination of CNS :

EEG:

Neuroimaging:

Hormone level:

MASTER CHART

S. NO.	AGE	TYPE OF SEIZURE			DURATION (YEARS)	TYPE		MENSTRUAL PERIOD		HORMONE LEVEL		EEG				CT / MRI	USG	ANTI CONVULSANTS			
		GTCS	ABSENCE	CPS		CE	NCE	REG	IRREG	EST	PRG	BSW	LTSW	RTSW	3SW			PHN+SVP	PHN+CBZ	CBZ+PHN+DZM	PHN+SVP+CBZ
1	22	1	0	0	6	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
2	35	0	0	1	7	0	1	1	0	0	0	1	0	0	0	N	N	0	1	0	0
3	19	0	1	0	8	0	1	1	0	0	0	0	0	0	1	N	N	0	0	0	1
4	26	0	0	1	5	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
5	23	0	0	1	4	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
6	36	1	0	0	9	1	0	1	0	0	0	0	0	1	0	N	N	1	0	0	0
7	40	1	0	0	5	0	1	1	0	0	0	1	0	0	0	N	N	0	1	0	0
8	26	1	0	0	4	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
9	25	1	0	0	5	1	0	1	0	160	8.97	1	0	0	0	N	N	1	0	0	0
10	40	0	0	1	13	0	1	0	0	0	0	1	0	0	0	N	N	0	0	1	0
11	36	0	0	1	12	1	0	0	1	0	0	1	0	0	0	N	N	1	0	0	0
12	45	1	0	0	12	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
13	45	1	0	0	8	0	1	1	0	0	0	0	0	1	0	N	N	0	1	0	0
14	38	0	0	1	9	0	1	0	1	0	0	0	1	0	0	N	N	1	0	0	0
15	28	0	0	1	7	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
16	26	0	0	1	5	0	1	1	0	0	0	0	0	1	0	N	N	0	1	0	0
17	28	1	0	0	3	0	1	1	0	0	0	0	1	0	0	N	N	1	0	0	0
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20	37	1	0	0	13	0	1	0	1	0	0	1	0	0	0	N	N	1	0	0	0
21	25	1	0	0	6	0	1	1	0	0	0	0	0	1	0	N	N	0	1	0	0
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24	19	0	0	1	5	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
25	26	0	0	1	7	0	1	1	0	137	14.33	0	1	0	0	N	N	1	0	0	0
26	31	0	0	1	8	0	1	1	0	0	0	1	0	0	0	N	N	0	1	0	0
27	25	1	0	0	6	0	1	1	0	0	0	0	1	0	0	N	N	0	0	1	0
28	45	1	0	0	12	0	1	0	1	0	0	0	0	1	0	N	N	0	0	0	1
29	39	1	0	0	13	1	0	0	1	0	0	1	0	0	0	N	N	1	0	0	0
30	37	0	0	1	9	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
31	27	1	0	0	8	0	1	1	0	135	14.25	0	1	0	0	N	N	0	0	0	1
32	17	0	1	0	4	0	1	1	0	0	0	0	0	0	1	N	N	0	0	0	1
33	45	1	0	0	17	0	1	1	0	0	0	0	0	1	0	N	N	0	1	0	0
34	43	0	0	1	9	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
35	48	0	0	1	13	0	1	0	0	0	0	0	1	0	0	N	N	0	0	1	0
36	27	0	0	1	8	1	0	1	0	253	9.24	1	0	0	0	N	N	0	0	0	1
37	19	1	0	0	5	1	0	1	0	263	8.07	1	0	0	0	N	N	1	0	0	0
38	38	1	0	0	7	0	1	0	0	0	0	0	0	1	0	N	N	0	1	0	0
39	28	0	0	1	4	0	1	0	1	0	0	1	0	0	0	N	N	1	0	0	0
40	26	0	0	1	7	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1

S. NO.	AGE	TYPE OF SEIZURE			DURATION (YEARS)	TYPE		MENSTRUAL PERIOD		HORMONE LEVEL		EEG				CT / MRI	USG	ANTI CONVULSANTS			
		GTCS	ABSENCE	CPS		CE	NCE	REG	IRREG	EST	PRG	BSW	LTSW	RTSW	3SW			PHN+SVP	PHN+CBZ	CBZ+PHN+DZM	PHN+SVP+CBZ
41	27	1	0	0	5	0	1	1	0	0	0	0	1	0	0	N	N	0	0	1	0
42	24	1	0	0	6	1	1	1	0	0	0	1	0	0	0	N	N	0	1	0	0
43	30	1	0	0	7	0	1	1	0	0	0	0	0	1	0	N	N	0	1	0	0
44	45	1	0	0	9	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
45	18	0	0	1	9	0	1	1	0	132	14.23	0	1	0	0	N	N	1	0	0	0
46	29	0	0	1	7	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
47	31	1	0	0	9	1	0	0	1	0	0	1	0	0	0	N	N	0	0	0	1
48	35	1	0	0	7	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
49	35	1	0	0	9	1	0	1	0	181	6.32	0	1	0	0	N	N	0	1	0	0
50	43	0	0	1	9	0	1	1	0	0	0	0	1	0	0	N	N	0	1	0	0
51	42	0	0	1	12	0	1	0	1	0	0	1	0	0	0	N	N	1	0	0	0
52	35	1	0	0	16	0	1	1	0	184	12.15	0	1	0	0	N	N	0	0	0	1
53	42	1	0	0	9	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
54	40	1	0	0	12	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
55	21	0	0	1	4	1	0	1	0	0	0	1	0	0	0	N	N	0	0	0	1
56	27	1	0	0	7	1	0	1	0	0	0	0	1	0	0	N	N	0	1	0	0
57	44	1	0	0	10	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
58	45	0	0	1	10	0	1	0	1	0	0	1	0	0	0	N	N	0	1	0	0
59	44	0	0	1	12	0	1	1	0	0	0	1	0	0	0	N	N	1	0	0	0
60	41	1	0	0	10	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
61	15	0	1	0	4	0	1	0	1	0	0	0	0	0	1	N	N	0	0	0	1
62	24	1	0	0	7	1	0	1	0	0	0	1	0	0	0	N	N	0	1	0	0
63	45	1	0	0	12	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
64	43	1	0	0	15	0	1	1	0	0	0	0	1	0	0	N	N	0	1	0	0
65	14	0	1	0	2	0	1	0	1	0	0	0	0	0	1	N	N	1	0	0	0
66	28	0	0	1	5	1	0	1	0	330	8.62	1	0	0	0	N	N	0	0	1	0
67	19	1	0	0	3	0	1	1	0	174	16.69	0	0	1	0	N	N	0	0	0	1
68	23	1	0	0	7	0	1	0	1	0	0	1	0	0	0	N	N	0	0	0	1
69	32	1	0	0	10	1	0	1	0	328	8.38	0	1	0	0	N	N	0	0	0	1
70	20	0	0	1	3	1	0	1	0	0	0	1	0	0	0	N	N	0	0	0	1
71	40	1	0	0	14	0	1	1	0	0	0	0	0	1	0	N	N	0	0	0	1
72	28	0	0	1	7	0	1	1	0	130	16.64	0	1	0	0	N	N	0	0	0	1
73	27	0	0	1	4	0	1	0	1	0	0	1	0	0	0	N	N	0	0	0	1
74	23	1	0	0	5	1	0	1	0	323	8.6	1	0	0	0	N	N	0	0	1	0
75	38	1	0	0	12	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
76	19	1	0	0	8	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
77	27	0	0	1	9	1	0	0	1	0	0	0	1	0	0	N	N	0	0	1	0
78	30	1	0	0	7	0	1	1	0	139	14.55	0	1	0	0	N	N	0	0	0	1
79	24	1	0	0	6	0	1	0	1	0	0	1	0	0	0	N	N	0	0	0	1
80	28	0	0	1	9	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1

S. NO.	AGE	TYPE OF SEIZURE			DURATION (YEARS)	TYPE		MENSTRUAL PERIOD		HORMONE LEVEL		EEG				CT / MRI	USG	ANTI CONVULSANTS			
		GTCS	ABSENCE	CPS		CE	NCE	REG	IRREG	EST	PRG	BSW	LTSW	RTSW	3SW			PHN+SVP	PHN+CBZ	CBZ+PHN+DZM	PHN+SVP+CBZ
81	23	0	0	1	8	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
82	39	1	0	0	15	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
83	30	1	0	0	12	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
84	18	0	1	0	9	0	1	1	0	0	0	0	0	0	1	N	N	0	0	0	1
85	20	0	0	1	6	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
86	42	1	0	0	9	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
87	40	0	0	1	15	0	1	0	1	0	0	0	0	1	0	N	N	0	0	0	1
88	30	0	0	1	8	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
89	15	0	1	0	4	0	1	1	0	0	0	0	0	0	1	N	N	0	0	0	1
90	24	0	0	1	5	0	1	1	0	175	16.09	1	0	0	0	N	N	0	0	0	1
91	15	0	0	1	3	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
92	14	0	0	1	3	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
93	16	0	0	1	4	0	1	1	0	0	0	0	1	0	0	N	N	0	0	0	1
94	45	0	0	1	20	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
95	24	0	0	1	6	1	0	0	1	0	0	0	1	0	0	N	N	0	0	0	1
96	41	0	0	1	18	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
97	20	0	1	0	8	1	0	0	1	0	0	0	0	0	1	N	N	0	0	0	1
98	19	0	0	1	8	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
99	29	0	0	1	10	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1
100	14	1	0	0	4	0	1	1	0	0	0	1	0	0	0	N	N	0	0	0	1

KEY TO MASTER CHART

0	–	No
1	–	Yes
GTCS	–	Generalised tonic clonic seizures
CPS	–	Complex partial seizures
CE	–	Catamenial Epilepsy
NCE	–	Non catamenial Epilepsy
REG	–	Regular menstrual cycle
IRREG	–	Irregular menstrual cycle
EST	–	Estradiol (pg/ml)
PRG	–	Progesterone (ng/ml)
BSW	–	Bursts of spike and wave discharges
LTSW	–	Left temporal spike and wave discharges
RTSW	–	Right temporal spike and wave discharges
3SW	–	3 cycles per second spike and wave discharges
PHN	–	Phenytoin
SVP	–	Sodium valproate
CBZ	–	Carbamazepine
DZM	–	Diazepam